

# **Exhibit A**

**UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

NATERA, INC.,	)	
	)	
<i>Plaintiff / Counterclaim-Defendant,</i>	)	
	)	
v.	)	C.A. No. 20-125-LPS
	)	
ARCHERDX, INC., ARCHERDX, LLC,	)	<b>JURY TRIAL DEMANDED</b>
INVITAE CORPORATION	)	
	)	
<i>Defendants / Counterclaimants.</i>	)	

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**DEFENDANTS INVITAE CORPORATION’S AND ARCHERDX, LLC’S FIRST  
AMENDED ANSWER AND COUNTERCLAIMS TO PLAINTIFF’S SECOND  
AMENDED COMPLAINT FOR PATENT INFRINGEMENT**

Defendants Invitae Corporation (“Invitae”) and ArcherDX, LLC (“ArcherDX”) (collectively, “Defendants”) hereby submit the following preliminary statement, answer, defenses (affirmative and otherwise), and counterclaims to Natera, Inc.’s (“Natera” or “Plaintiff”) Second Amended Complaint (D.I. 116) filed on January 12, 2021.

**PRELIMINARY STATEMENT**

a. Invitae is a leading medical genetics company whose mission is to bring comprehensive genetic information into mainstream medicine to improve healthcare for billions of people. Invitae’s goal is to aggregate the world’s genetic tests into a single service with higher quality, faster turnaround time, and lower prices.

b. ArcherDX is a leading genomics company democratizing precision oncology, including the use of genetic information from genomic tumor profiling to guide cancer therapy optimization and monitoring. ArcherDX offers a suite of innovative products and services that are highly accurate, personal, actionable, and easy to use in local settings.

c. With its proprietary product development platform, ArcherDX is developing

industry-leading products and services to optimize therapy and monitor cancer. Specifically, ArcherDX is in the process of developing *in vitro* diagnostic (“IVD”) products for approval or clearance by the United States Food and Drug Administration (“FDA”). For example, STRATAFIDE™ is in development as a universal IVD and companion diagnostic product. STRATAFIDE™ has twice received Breakthrough Device designation from the FDA. In January 2020, ArcherDX also received Breakthrough Device designation from the FDA for its Personalized Cancer Monitoring product, PCM, which it is developing as an IVD to non-invasively and quantitatively measure cancer recurrence or progression, as well as therapeutic efficacy.

d. Natera’s U.S. Patent Nos. 10,538,814 (“the ’814 Patent”), 10,557,172 (“the ’172 patent”), 10,590,482 (“the ’482 patent”) (collectively, “the Asserted cfDNA Patents”), 10,597,708 (“the ’708 patent”), and 10,731,220 (“the ’220 patent”) (together with the Asserted cfDNA Patents, the “Asserted Patents”) stem from protracted and convoluted prosecutions at the U.S. Patent and Trademark Office (“USPTO”). Over the course of a decade, Natera filed a plethora of provisional, continuation, and continuation-in-part patent applications, and it abandoned many of them. In connection with those applications, Natera filed *hundreds* of proposed claims with the USPTO and disclosed *thousands* of references. But Natera did not disclose key prior art that discloses or renders obvious the claimed methods for amplifying and sequencing nucleic acids.

e. Moreover, despite this protracted and convoluted prosecution history, prior to April 30, 2019, when it filed the applications that resulted in the Asserted Patents, Natera had *never* disclosed nor sought to patent the methods recited in the claims of the Asserted Patents. Indeed, that is because Natera did not invent those methods; tellingly, Natera does not allege in its Second Amended Complaint that it even practices the methods claimed in the Asserted Patents.

f. Instead, on information and belief, Natera is a copyist that drafted claims designed to cover ArcherDX's proprietary Anchored Multiplex PCR ("AMP<sup>TM</sup>") processes—after being outcompeted in the marketplace; ArcherDX's proprietary AMP<sup>TM</sup> processes are technologically and commercially superior to Natera's legacy technology.

g. Notably, Natera filed the applications leading to the Asserted Patents shortly after it gained access to confidential information relating to ArcherDX's products, including LIQUIDPlex<sup>TM</sup>, STRATAFIDE<sup>TM</sup>, and PCM.

h. As described below, Natera's efforts to stymie ArcherDX's technological advantage violate the patent laws on multiple levels: the belatedly drafted claims fail to satisfy the substantive requirements of patentability, including 35 U.S.C. §§ 101, 102, 103, and/or 112; no one associated with Natera invented the claimed methods; and Natera's unreasonable delay in prosecution—coupled with its filings of the applications leading to the Asserted Patents soon after it gained access to ArcherDX's confidential information and for the purpose of attempting to unjustifiably regain traction in the marketplace—trigger the doctrines of unclean hands and prosecution laches, barring Natera's infringement claims.

i. In any event, Natera is a poor copyist. The Defendants do not practice the technology claimed in any of the Asserted Patents, and therefore does not infringe. Moreover, activities complained of by Natera are protected by the safe harbor of 35 U.S.C. § 271(e)(1) and, accordingly, immune from infringement claims.

j. In an attempt to harass and cast a cloud over ArcherDX, Natera improperly seeks a preliminary and inappropriate advisory opinion from the Court regarding ArcherDX's STRATAFIDE<sup>TM</sup> and PCM products, which are still in the development stage—without an application for FDA approval even on file.



k. Finally, Natera moved to add Invitae as a party to its Second Amended Complaint in its attempt to cast a wide net of blame, even though Invitae did not develop the accused products.

l. In sum, Natera's meritless Second Amended Complaint represents a last-ditch effort to bully a smaller, technologically advanced company using the courtroom, because Natera fears it will be unable to succeed with its inferior products in the marketplace.

### **ANSWER**

The Defendants deny all allegations in the Second Amended Complaint, whether express or implied, that are not specifically admitted below, including all allegations in any headings or unnumbered paragraphs. The Defendants further deny that Natera is entitled to the requested relief or any other relief.

### **OVERVIEW OF THE ACTION**<sup>1</sup>

1. The Defendants expressly deny that any ArcherDX product falls within the alleged scope of any claim of the '814 Patent, the '172 Patent, the '482 Patent, the '708 Patent, and the '220 patent, and that any of its activities constitute "infringement of Natera's innovative, patented technology." The Defendants admit that the Second Amended Complaint purports to state an action for infringement of the '814 Patent, the '172 Patent, the '482 Patent, the '708 Patent, and the '220 Patent. The Defendants admit that LIQUIDPlex<sup>TM</sup> was previously called Reveal ctDNA. LIQUIDPlex<sup>TM</sup> is a product sold for research use only, and it uses ArcherDX's proprietary AMP<sup>TM</sup> chemistry. FusionPlex<sup>®</sup> and VariantPlex<sup>®</sup> are also products sold for research use only, and use ArcherDX's proprietary AMP<sup>TM</sup> chemistry. Besides LIQUIDPlex<sup>TM</sup>,

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<sup>1</sup> For the Court's convenience, the Defendants generally adopt the headings used in Natera's Second Amended Complaint. In so doing, the Defendants do not admit that the headings are accurate, and reserves the right to contest any statement or characterization set forth under them. To the extent the headings constitute allegations requiring a response, they are denied.

FusionPlex<sup>®</sup> and VariantPlex<sup>®</sup>, ArcherDX does not sell, or have in development, any other products for research use only that use ArcherDX's proprietary AMP<sup>™</sup> chemistry. The Defendants further admit that ArcherDX is currently developing its STRATAFIDE<sup>™</sup> and PCM products for approval or clearance by the FDA. The Defendants further admit that Archer<sup>®</sup>MET is an IVD product that has been approved in Japan only. The Defendants deny the allegation that ArcherDX "does not have freedom to operate its AMP products for minimal residual disease ("MRD") and personalized cancer monitoring." The Defendants further deny each and every allegation of paragraph 1 of the Second Amended Complaint.

### **THE PARTIES**

2. The Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 2 of the Second Amended Complaint, and therefore denies each and every allegation in that paragraph.

3. Paragraph 3 of the Second Amended Complaint contains statements of opinion to which no response is required. To the extent paragraph 3 contains factual allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of those allegations, and therefore denies each and every allegation in that paragraph.

4. Paragraph 4 of the Second Amended Complaint contains statements of opinion to which no response is required. To the extent paragraph 4 contains factual allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of those allegations, and therefore denies each and every allegation in that paragraph.

5. Paragraph 5 of the Second Amended Complaint contains statements of opinion to which no response is required. To the extent paragraph 5 contains factual allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of those allegations, and therefore denies each and every allegation in that paragraph.

6. Paragraph 6 of the Second Amended Complaint contains statements of opinion to which no response is required. To the extent paragraph 6 contains factual allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of those allegations, and therefore denies each and every allegation in that paragraph.

7. Paragraph 7 of the Second Amended Complaint contains statements of opinion to which no response is required. To the extent paragraph 7 contains factual allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of those allegations, and therefore denies each and every allegation in that paragraph.

8. Paragraph 8 of the Second Amended Complaint contains statements of opinion to which no response is required. To the extent paragraph 8 contains factual allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of those allegations, and therefore denies each and every allegation in that paragraph.

9. The Defendants deny the allegations of paragraph 9 of the Second Amended Complaint. The Defendants specifically deny that ArcherDX has committed the alleged acts of infringement and further denies that any Asserted Patent claims an “invention.” The Defendants aver that all Asserted Patents are invalid for failure to satisfy one or more conditions for patentability set forth under 35 U.S.C. including but not limited to §§ 101, 102, 103, and 112 et seq.; no one associated with Natera invented the claimed methods; and the Asserted Patents are unenforceable against the Defendants by reason of Natera’s unclean hands and prosecution laches.

10. ArcherDX admits that ArcherDX, Inc. was, at the time of the filing of this action, a corporation organized and existing under the laws of the State of Delaware, having a place of business at 2477 55th Street, Suite 202, Boulder, Colorado 80301. ArcherDX admits that

ArcherDX, LLC is a limited liability company, organized and existing under the laws of the State of Delaware.

11. Invitae admits that it is a corporation organized and existing under the laws of the States of Delaware, having a principal place of business at 1400 16th Street, San Francisco, CA 94103.

12. The Defendants admit that Invitae's Form 8-K, filed on October 5, 2020, indicates that on October 2, 2020, Invitae consummated the acquisition of ArcherDX, Inc., from which ArcherDX, LLC became a wholly-owned subsidiary of Invitae.

13. The Defendants admit that it represented that effective October 2, 2020, Defendant ArcherDX Inc. merged with Apollo Merger Sub A Inc., which then merged with Apollo Merger Sub B LLC to form ArcherDX, LLC (referenced herein as "ArcherDX"). The Defendants admit that the Court has substituted ArcherDX, LLC for ArcherDX, Inc.

14. Paragraph 14 of the Second Amended Complaint contains statements of opinion and legal conclusions to which no response is required. To the extent paragraph 14 excerpts the contents of an Invitae document, the document speaks for itself. Except as expressly admitted herein, to the extent a response is required, ArcherDX denies each and every allegation in paragraph 14 of the Second Amended Complaint.

15. The Defendants deny the allegations of paragraph 15 of the Second Amended Complaint. ArcherDX independently developed its own proprietary AMP<sup>TM</sup> chemistry, technology platform, and applications, which are covered by three issued patents and 15 pending patent applications in the United States and two issued patents and 43 pending patent applications in foreign countries.

### **JURISDICTION AND VENUE**

16. The allegation of jurisdiction in paragraph 16 of the Second Amended Complaint constitutes a legal conclusion that requires no response. To the extent a response is required, the Defendants admit that the Second Amended Complaint purports to state an action that arises under the patent laws of the United States, 35 U.S.C. § 1, et seq. The Defendants specifically deny that the Second Amended Complaint states a claim upon which relief may be granted.

17. The allegation of jurisdiction in paragraph 17 of the Second Amended Complaint constitutes a legal conclusion that requires no response. To the extent a response is required, the Defendants admit that the Second Amended Complaint purports to state an action that arises under 28 U.S.C. §§ 1331 and 1338(a), and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202. The Defendants specifically deny that the Second Amended Complaint states a claim upon which relief may be granted. The Defendants further deny that the Second Amended Complaint pleads the existence of a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act with respect to ArcherDX's yet-to-be-FDA-approved IVD products (or any other oncology product in development or used overseas, and that utilizes the same technology as any of the Accused Products). Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 16.

18. The allegation of jurisdiction in paragraph 18 of the Second Amended Complaint constitutes a legal conclusion that requires no response. To the extent a response is required, the Defendants do not contest that this Court has personal jurisdiction over the Defendants for purposes of this action. ArcherDX admits that ArcherDx, Inc. was, at the time of the filing of this action, a corporation organized and existing under the laws of the State of Delaware, having a place of business at 2477 55th Street, Suite 202, Boulder, Colorado 80301. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 18.

19. The allegation of jurisdiction in paragraph 19 of the Second Amended Complaint constitutes a legal conclusion that requires no response. To the extent a response is required, the Defendants do not contest that this Court has personal jurisdiction over ArcherDX for purposes of this action. The Defendants specifically deny that ArcherDX has committed the alleged acts of infringement in this District or anywhere else. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 19.

20. The allegation of jurisdiction in paragraph 20 of the Second Amended Complaint constitutes a legal conclusion that requires no response. To the extent a response is required, the Defendants do not contest that this Court has personal jurisdiction over ArcherDX for purposes of this action. ArcherDX admits that it initiated the civil action *ArcherDX, Inc. et al v. Qiagen Sciences, LLC et al.*, 18-1019-MN (D. Del. 2018). Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 20.

21. The allegation of jurisdiction in paragraph 21 of the Second Amended Complaint constitutes a legal conclusion that requires no response. To the extent a response is required, the Defendants do not contest that this Court has personal jurisdiction over Invitae for purposes of this action. The Defendants specifically deny that Invitae has committed the alleged acts of infringement in this District or anywhere else. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 19.

22. The allegation of jurisdiction in paragraph 22 of the Second Amended Complaint constitutes a legal conclusion that requires no response. To the extent a response is required, the Defendants do not contest that this Court has personal jurisdiction over ArcherDX for purposes of this action. ArcherDX admits that ArcherDX, Inc. was, at the time of the filing of the action, a corporation organized and existing under the laws of the State of Delaware, having a place of

business at 2477 55<sup>th</sup> Street, Suite 202, Boulder, Colorado 80301. The Defendants do not contest that this Court has personal jurisdiction over Invitae for the purposes of this action. Invitae admits that it is a corporation organized and existing under the laws of the State of Delaware. Except as expressly admitted herein, ArcherDX denies each and every allegation of paragraph 22.

23. The allegation of jurisdiction in paragraph 23 of the Second Amended Complaint constitutes a legal conclusion that requires no response. To the extent a response is required, the Defendants do not contest that this Court has personal jurisdiction over Invitae for the purposes of this action. The Defendants specifically deny that the Defendants have committed the alleged acts of infringement in this District or anywhere else and also deny that Invitae is vicariously liable for any alleged infringing acts. The Defendants expressly deny that Invitae is the alter ego of ArcherDX. To the extent paragraph 23 excerpts the contents of an Invitae document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 23.

24. The Defendants admit that Natera accurately quoted Invitae's Form S-4 filed with the Securities and Exchange Commission on August 25, 2020. Except as expressly admitted herein, ArcherDX denies each and every allegation of paragraph 24.

25. The Defendants admit that Natera correctly quoted the prospectus for the merger. The Defendants deny that the emphasis indicated in the quoted language is accurate. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 25.

26. The Defendants deny that a "10-02-2020 Form 8-K" issued by Invitae exists as alleged. To the extent Natera intended to indicate Invitae's Form 8-K filed on a different date, the Defendants reserve the right to respond to any modification or clarification. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 26.

27. The Defendants admit that the web address <https://archerdx.com/> displays ArcherDX's and Invitae's names and logos, states that "The Invitae-ArcherDX combination has now closed" and "We're Right Where You Need Us." Any other statements in paragraph 27 of the Second Amended Complaint contains statements of opinion to which no response is required. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 27.

28. The Defendants admit that the article cited by Natera is accurately quoted in paragraph 28. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 28.

29. The Defendants admit that Jason Myers, former CEO of ArcherDX, Inc., currently serves as Invitae's President of Oncology and sits on the Invitae Board of Directors. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 29.

30. The allegation of venue in paragraph 30 of the Second Amended Complaint constitutes a legal conclusion that requires no response. To the extent a response is required, the Defendants do not contest that, for the purposes of this action, and without waiving any defense of improper venue in connection with any other cause of action or claim, venue properly lies in this judicial district pursuant to 28 U.S.C. § 1400(b). The Defendants admit that ArcherDX, Inc. is a Delaware corporation. Except as expressly admitted herein, the Defendants further deny each and every allegation of paragraph 30.

31. The allegation of venue in paragraph 30 of the Second Amended Complaint constitutes a legal conclusion that requires no response. To the extent a response is required, the Defendants do not contest that, for the purposes of this action, and without waiving any defense of improper venue in connection with any other cause of action or claim, venue properly lies in



this judicial district pursuant to 28 U.S.C. § 1400(b). The Defendants admit that Invitae is a Delaware corporation. Except as expressly admitted herein, the Defendants further deny each and every allegation of paragraph 31.

### **BACKGROUND**

32. Paragraph 32 of the Second Amended Complaint contains statements of opinion to which no response is required. To the extent paragraph 32 contains factual allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of those allegations, and therefore deny each and every allegation in that paragraph.

33. Paragraph 33 of the Second Amended Complaint contains statements of opinion to which no response is required. To the extent paragraph 33 contains factual allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of those allegations, and therefore deny each and every allegation in that paragraph.

34. Paragraph 34 of the Second Amended Complaint contains statements of opinion to which no response is required. To the extent paragraph 34 contains factual allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of those allegations, and therefore deny each and every allegation in that paragraph.

35. Paragraph 35 of the Second Amended Complaint contains statements of opinion to which no response is required. To the extent paragraph 35 contains factual allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations, and therefore deny each and every allegation in that paragraph.

36. Paragraph 36 of the Second Amended Complaint contains statements of opinion to which no response is required. To the extent paragraph 36 contains factual allegations, Naterra does not identify any particular “MRD assessment” in paragraph 36, and accordingly the

Defendants are without knowledge or information sufficient to form a belief as to the truth of those allegations, and therefore deny each and every allegation in that paragraph.

37. Paragraph 37 of the Second Amended Complaint contains statements of opinion to which no response is required. To the extent paragraph 37 contains factual allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of those allegations, and therefore deny each and every allegation in that paragraph.

38. Paragraph 38 of the Second Amended Complaint contains statements of opinion to which no response is required. To the extent paragraph 38 contains factual allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of those allegations, and therefore deny each and every allegation in that paragraph.

39. Paragraph 39 of the Second Amended Complaint contains statements of opinion to which no response is required. To the extent paragraph 39 contains factual allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations, and therefore deny each and every allegation in that paragraph.

40. Paragraph 40 of the Second Amended Complaint contains statements of opinion to which no response is required. To the extent paragraph 40 contains factual allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of those allegations, and therefore deny each and every allegation in that paragraph.

41. The Defendants deny that the Asserted Patents relate to “innovative new methods for amplifying and sequencing nucleic acids, including cell-free DNA.” The Defendants further denies that the claims of the Asserted Patents recite methods that are novel or innovative. The Defendants aver that all Asserted Patents are invalid for failure to satisfy one or more conditions for patentability set forth under 35 U.S.C. including but not limited to §§ 101, 102, 103, and 112

et seq.; no one associated with Natera invented the claimed methods; and the Asserted Patents are unenforceable against the Defendants by reason of Natera's unclean hands and prosecution laches. Except as expressly denied herein, the Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 41 of the Second Amended Complaint, and therefore deny each and every allegation in that paragraph.

### **GENERAL BACKGROUND OF THE ASSERTED PATENTS**

42. The Defendants admit that a document purporting to be a copy of the '814 Patent is attached to the Second Amended Complaint as Exhibit 1. The Defendants admit that, on its face, the '814 Patent, titled "Methods for Simultaneous Amplification of Target Loci," indicates that it was issued by the USPTO on January 21, 2020. As to the remaining allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 42 of the Second Amended Complaint, and therefore deny each and every allegation of that paragraph.

43. The Defendants admit that claim 1 of the '814 Patent recites:

A method for amplifying and sequencing DNA, comprising:

ligating adaptors to cell-free DNA isolated from a biological sample, wherein the adaptors each comprises a universal priming site;

performing a first PCR to simultaneously amplify at least 10 target loci using a universal primer and at least 10 target-specific primers in a single reaction volume;

performing a second, nested PCR to simultaneously amplify the at least 10 target loci using the universal primer and at least 10 inner target-specific primers in a single reaction volume, wherein at least one of the primers comprises a sequencing tag;

performing high-throughput sequencing to sequence the amplified DNA comprising the target loci.

The Defendants admit that claim 1 recites a "method for amplifying and sequencing DNA" and further recites "PCR" and "high-throughput sequencing." Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 43 of the Second Amended Complaint.

44. The Defendants admit that a document purporting to be a copy of the '172 Patent is attached to the Second Amended Complaint as Exhibit 2. The Defendants admit that, on its face, the '172 Patent, titled "Methods for Simultaneous Amplification of Target Loci," indicates that it was issued by the USPTO on February 11, 2020. As to the remaining allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 44 of the Second Amended Complaint, and therefore deny each and every allegation of that paragraph.

45. The Defendants admit that claim 1 of the '172 Patent recites:

A method for amplifying and sequencing DNA, comprising:

isolating cell-free DNA from a biological sample and tagging the isolated cell-free DNA, wherein each tagged DNA molecule comprises a molecular barcode;

performing a first PCR to simultaneously amplify at least 10 target loci using a universal primer and at least 10 target-specific primers in a single reaction volume;

performing a second, nested PCR to simultaneously amplify the at least 10 target loci using the universal primer and at least 10 inner target-specific primers in a single reaction volume;

performing high-throughput sequencing to sequence the amplified DNA comprising the target loci.

The Defendants admit that claim 1 recites a "method for amplifying and sequencing DNA" and further recites "PCR" and "high-throughput sequencing." Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 45 of the Second Amended Complaint.

46. The Defendants admit that a document purporting to be a copy of the '482 Patent is attached to the Second Amended Complaint as Exhibit 3. The Defendants admit that, on its face, the '482 Patent, titled "Amplification of cell-free DNA using nested PCR," indicates that it was issued by the USPTO on March 17, 2020. As to the remaining allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations

of paragraph 46 of the Second Amended Complaint, and therefore deny each and every allegation of that paragraph.

47. The Defendants deny that the claim language recited in paragraph 47 of the Amended Complaint reflects claim 1 of the '482 Patent. The Defendants admit that claim 1 of the '482 Patent actually recites:

A method for nested PCR amplification, comprising:  
isolating cell-free DNA from a biological sample and ligating adaptors to the isolated cell-free DNA, wherein the adaptors each comprise a universal priming site;  
performing a first PCR to simultaneously amplify at least 10 target loci using a universal primer and at least 10 target-specific primers in a first reaction volume; and  
performing a second, nested PCR to simultaneously amplify the at least 10 target loci using the universal primer and at least 10 inner target-specific primers in a second reaction volume to obtain amplified DNA, wherein primer binding sites of the inner target-specific primers of the second PCR are internal to primer binding sites of the target-specific primers of the first PCR, wherein at least 80% of the amplified DNA maps to the target loci.

The Defendants admit that claim 1 recites a “method for nested PCR amplification” and further recites “a first reaction volume” and “a second reaction volume.” Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 47 of the Second Amended Complaint.

48. The Defendants admit that a document purporting to be a copy of the '708 Patent is attached to the Second Amended Complaint as Exhibit 4. The Defendants admit that, on its face, the '708 Patent, titled “Methods for Simultaneous Amplifications of Target Loci,” indicates that it was issued by the USPTO on March 24, 2020. As to the remaining allegations, the Defendants is without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 48 of the Second Amended Complaint, and therefore deny each and every allegation of that paragraph.

49. The Defendants admit that claim 1 of the '708 Patent recites:

A method for amplifying target loci in a nucleic acid sample, comprising:  
contacting the nucleic acid sample comprising target loci with a library of at least 2 primers that simultaneously hybridize to at least 2 of the target loci to produce a reaction mixture;  
subjecting the reaction mixture to primer extension reaction conditions to produce amplified products comprising target amplicons; wherein the annealing temperature for the reaction conditions is greater than a melting temperature of the at least 2 primers, wherein the length of the annealing step of the reaction conditions is greater than 3 minutes, and wherein the at least 2 of the target loci are simultaneously amplified; and  
sequencing the amplified products.

The Defendants admit that claim 1 recites “a method for amplifying target loci in a nucleic acid sample” and further recites “a reaction mixture” and “reaction conditions.” Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 49 of the Second Amended Complaint.

50. The Defendants admit that a document purporting to be a copy of the '220 Patent is attached to the *Natera, Inc. v. ArcherDX, Inc.*, Case No. 20-cv-1047 (D. Del.), Complaint as Exhibit 5. The Defendants admit that, on its face, the '220 Patent, titled “Methods for Simultaneous Amplification of Target Loci,” indicates that it was issued by the USPTO on August 4, 2020. As to the remaining allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 50 of the Second Amended Complaint, and therefore deny each and every allegation in that paragraph.

51. The Defendants admit that Natera, Inc. is listed as the assignee on the face of the '220 Patent. The Defendants deny that the '220 Patent is valid and enforceable. The Defendants aver that the '220 Patent is invalid for failure to satisfy one or more conditions for patentability set forth under 35 U.S.C. including but not limited to §§ 101, 102, 103, and 112 et seq.; no one associated with Natera invented the claimed methods; and the '220 Patent is unenforceable against

the Defendants by reason of Natera's inequitable conduct, unclean hands, and prosecution laches. As to the remaining allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 51 of the Second Amended Complaint, and therefore deny each and every allegation in that paragraph.

52. The Defendants admit that, on its face, the '220 Patent states that it issued from Application No. 16/743,724 and lists a filing date of January 15, 2020. The Defendants admit that, on its face, the '220 Patent states that it is a continuation of Application No. 16/399,268, which is a continuation of Application 16/140,298, which is a continuation of Application No. 14/918,544 filed on October 20, 2015. As to the remaining allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 52 of the Second Amended Complaint, and therefore deny each and every allegation in that paragraph.

53. The Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 53 of the Second Amended Complaint, and therefore deny each and every allegation in that paragraph.

54. The Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 54 of the Second Amended Complaint, and therefore deny each and every allegation in that paragraph.

55. The Defendants admit that claim 1 of the '220 Patent recites:

A method for amplifying and sequencing DNA, comprising:

ligating adaptors to cell-free DNA isolated from a biological sample, wherein the adaptors each comprises a universal priming sequence and a molecular barcode; performing a first PCR to simultaneously amplify at least 10 target loci using a universal primer and at least 10 target-specific primers in a single reaction volume; performing a second, nested PCR to simultaneously amplify the at least 10 target loci using a second universal primer and at least 10

inner target-specific primers in a single reaction volume, wherein at least one of the primers comprises a sequencing tag; performing high-throughput sequencing to sequence the amplified DNA comprising the target loci.

The Defendants admit that claim 1 nominally recites a “method for amplifying and sequencing DNA” and further nominally recites “PCR” and “high-throughput sequencing.” Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 55 of the Second Amended Complaint.

56. Paragraph 56 of the Second Amended Complaint contains statements of opinion and legal conclusions to which no response is required. To the extent a response is required, the Defendants deny each and every allegation in that paragraph. Indeed, as set forth in the Defendants’ Counterclaims, Natera’s own admissions made in court filings in this District and elsewhere contradict the allegations of paragraph 35 of the Second Amended Complaint. The Defendants expressly deny that “the claims of the ’814 patent cover methods of preparation,” and further deny that such claims are analogous to claims that “were held not [to] be directed to a natural law or phenomenon in the recent Federal Circuit decision in *Illumina, Inc. v. Ariosa Diagnostics, Inc.*,” 952 F.3d 1367 (Fed. Cir. 2020).

57. Paragraph 57 of the Second Amended Complaint contains statements of opinion and legal conclusions to which no response is required. To the extent a response is required, the Defendants deny each and every allegation in that paragraph. Indeed, as set forth in the Defendants’ Counterclaims, Natera’s own admissions made in court filings in this District and elsewhere contradict the allegations of paragraph 57 of the Second Amended Complaint.

58. The Defendants admit the language appearing in the block quote in paragraph 58 of the Second Amended Complaint reflects a statement made by the USPTO examiner during the prosecution of the ’814 Patent. The Defendants deny the allegation that “the USPTO examiner



found the claims to be non-routine and non-conventional.” Indeed, as set forth in the Defendants’ Counterclaims, Natera’s own admissions made in court filings in this District and elsewhere contradict the allegations of paragraph 58. Moreover, the Defendants aver that, contrary to the USPTO examiner’s statement, “amplification of . . . circulating nucleic acids” is disclosed in the prior art, including in U.S. Patent App. Pub. No. 2010/0120038 (“Mir”). The Defendants further aver that “sequencing steps, . . . incorporat[ing] a universal or common primer, and . . . a sequencing tag” are also disclosed in the prior art, including in Mir. Natera disclosed Mir as one of *thousands* of references disclosed during prosecution of the ’814 Patent.

59. The Defendants deny each and every allegation of paragraph 59 of the Second Amended Complaint.

60. Paragraph 60 of the Second Amended Complaint contains statements of opinion and legal conclusions to which no response is required. To the extent a response is required, the Defendants deny each and every allegation in that paragraph. Indeed, as set forth in the Defendants’ Counterclaims, Natera’s own admissions made in court filings in this District and elsewhere contradict the allegations of paragraph 60 of the Second Amended Complaint. The Defendants expressly deny that “the claims of the ’172 patent cover methods of preparation,” and further deny that such claims are analogous to claims that “were held not [to] be directed to a natural law or phenomenon in the recent Federal Circuit decision in *Illumina, Inc. v. Ariosa Diagnostics, Inc.*,” 952 F.3d 1367 (Fed. Cir. 2020).

61. Paragraph 61 of the Second Amended Complaint contains statements of opinion and legal conclusions to which no response is required. To the extent a response is required, the Defendants deny each and every allegation in that paragraph. Indeed, as set forth in the

Defendants' Counterclaims, Natera's own admissions made in court filings in this District and elsewhere contradict the allegations of paragraph 61 of the Second Amended Complaint.

62. The Defendants admit the language appearing in the block quote in paragraph 62 of the Second Amended Complaint reflects a statement made by the USPTO examiner during the prosecution of the '172 Patent. The Defendants deny the allegation that "the USPTO examiner found the claims to be non-routine and non-conventional." Indeed, as set forth in the Defendants' Counterclaims, Natera's own admissions made in court filings in this District and elsewhere contradict the allegations of paragraph 62. Moreover, the Defendants aver that, contrary to the USPTO examiner's statement, "amplification of . . . circulating nucleic acids" is disclosed in the prior art, including in Mir. The Defendants further aver that "sequencing steps, . . . incorporat[ing] a universal or otherwise common primer" are also disclosed in the prior art, including in Mir. Natera disclosed Mir as one of *thousands* of references disclosed during prosecution of the '172 Patent.

63. Paragraph 63 of the Second Amended Complaint contains statements of opinion and legal conclusions to which no response is required. To the extent a response is required, the Defendants deny each and every allegation in that paragraph. Indeed, as set forth in the Defendants' Counterclaims, Natera's own admissions made in court filings in this District and elsewhere contradict the allegations of paragraph 63 of the Second Amended Complaint. The Defendants expressly deny that "the claims of the '482 patent cover methods of preparation," and further deny that such claims are analogous to claims that "were held not [to] be directed to a natural law or phenomenon in the recent Federal Circuit decision in *Illumina, Inc. v. Ariosa Diagnostics, Inc.*," 952 F.3d 1367 (Fed. Cir. 2020).

64. Paragraph 64 of the Second Amended Complaint contains statements of opinion and legal conclusions to which no response is required. To the extent a response is required, the Defendants deny each and every allegation in that paragraph. Indeed, as set forth in the Defendants' Counterclaims, Natera's own admissions made in court filings in this District and elsewhere contradict the allegations of paragraph 64 of the Second Amended Complaint.

65. The Defendants admit the language appearing in the block quote in paragraph 65 of the Second Amended Complaint reflects a statement made by the USPTO examiner during the prosecution of the '482 Patent. The Defendants deny the allegation that "the USPTO examiner found the claims to be non-routine and non-conventional." Indeed, as set forth in the Defendants' Counterclaims, Natera's own admissions made in court filings in this District and elsewhere contradict the allegations of paragraph 65. Moreover, the Defendants aver that, contrary to the USPTO examiner's statement, "'nested PCR' following the recited 'first PCR' of 'cell-free DNA'" is disclosed in the prior art, including in Mir. Natera disclosed Mir as one of *thousands* of references disclosed during prosecution of the '482 Patent.

66. Paragraph 66 of the Second Amended Complaint contains statements of opinion and legal conclusions to which no response is required. To the extent a response is required, the Defendants deny each and every allegation in that paragraph. Indeed, as set forth in the Defendants' Counterclaims, Natera's own admissions made in court filings in this District and elsewhere contradict the allegations of paragraph 66 of the Second Amended Complaint. The Defendants expressly deny that "the claims of the '708 patent cover methods of preparation," and further deny that such claims are analogous to claims that "were held not [to] be directed to a natural law or phenomenon in the recent Federal Circuit decision in *Illumina, Inc. v. Ariosa Diagnostics, Inc.*," 952 F.3d 1367 (Fed. Cir. 2020).

67. Paragraph 67 of the Second Amended Complaint contains statements of opinion and legal conclusions to which no response is required. To the extent a response is required, the Defendants deny each and every allegation in that paragraph. Indeed, as set forth in the Defendants' Counterclaims, Natera's own admissions made in court filings in this District and elsewhere contradict the allegations of paragraph 67 of the Second Amended Complaint.

68. The Defendants admit the language appearing in the block quote in paragraph 68 of the Second Amended Complaint reflects a statement made by the USPTO examiner during the prosecution of the '708 Patent. The Defendants deny the allegation that "the USPTO examiner found the claims to be non-routine and non-conventional." Indeed, as set forth in the Defendants' Counterclaims, Natera's own admissions made in court filings in this District and elsewhere contradict the allegations of paragraph 68. Moreover, the Defendants aver that, contrary to the USPTO examiner's statement, "the selection of an annealing temperature higher than the melting temperature of the primers, the selection of a long annealing time and sequencing of the amplification products" is disclosed in the prior art, including in International App. No. WO 2013/169339 ("Iafrate") and U.S. Patent App. Pub. No. 2012/270212 ("Rabinowitz"). Natera disclosed a related Iafrate application (U.S. Patent App. Pub. No. 2013/0303461) and Rabinowitz as two of *thousands* of references disclosed during prosecution of the '708 Patent.

69. Paragraph 69 of the Second Amended Complaint contains statements of opinion and legal conclusions to which no response is required. To the extent a response is required, the Defendants deny each and every allegation in paragraph 69 of the Complaint. Indeed, as set forth in the Defendants' Counterclaims, Natera's own admissions made in court filings in this District and elsewhere contradict the allegations of paragraph 69 of the Complaint. The Defendants expressly denies that "[t]he claims are directed to an improved process of preparing non-natural

DNA,” and further deny that such claims are analogous to claims that were “found patentable in *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 967 F.3d 1319 (Fed. Cir. Aug. 3, 2020).”

70. Paragraph 70 of the Second Amended Complaint contains statements of opinion and legal conclusions to which no response is required. To the extent paragraph 70 excerpts the ’220 Patent, the document speaks for itself. Except as expressly admitted herein, to the extent a response is required, the Defendants deny each and every allegation in paragraph 70 of the Second Amended Complaint.

71. Paragraph 71 of the Second Amended Complaint contains statements of opinion and legal conclusions to which no response is required. To the extent a response is required, the Defendants deny each and every allegation in that paragraph. Indeed, as set forth in the Defendants’ Counterclaims, Natera’s own admissions made in court filings in this District and elsewhere contradict the allegations of paragraph 71 of the Second Amended Complaint.

72. Paragraph 72 of the Second Amended Complaint contains statements of opinion and legal conclusions to which no response is required. To the extent a response is required, the Defendants deny each and every allegation in that paragraph. Indeed, as set forth in the Defendants’ Counterclaims, Natera’s own admissions made in court filings in this District and elsewhere contradict the allegations of paragraph 72 of the Second Amended Complaint.

73. The Defendants admit the language appearing in the block quote in paragraph 73 of the Second Amended Complaint reflects a statement made by the USPTO examiner during the prosecution of the ’220 Patent. To the extent a response is required, the Defendants deny each and every allegation in paragraph 73 of the Second Amended Complaint. The Defendants specifically deny the allegation that “the USPTO examiner found the claims to be non-routine and non-conventional.” Indeed, as set forth in the Defendants’ Counterclaims, Natera’s own

admissions made in court filings in this District and elsewhere contradict the allegations of paragraph 73. Moreover, the Defendants aver that, contrary to the USPTO examiner's statement, "multiplex using universal or common primers, and a second step of nested amplification" is disclosed in the prior art, including in U.S. Patent App. Pub. No. 2010/0120038 ("Mir"). Natera disclosed Mir as one of thousands of references during prosecution of the '220 Patent.

74. Paragraph 74 of the Second Amended Complaint contains statements of opinion and legal conclusions to which no response is required. To the extent a response is required, the Defendants deny each and every allegation in paragraph 74 of the Second Amended Complaint.

### **ARCHERDX'S ALLEGED INFRINGING ACTIVITIES**

75. The Defendants deny that it and/or its end-users "perform every step of claim 1 of the Asserted Patents when they use any of the Accused Products." To the extent that paragraph 75 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 75 of the Second Amended Complaint.

76. The Defendants admit that ArcherDX, Inc. operates a CLIA-certified laboratory. The Defendants deny that they perform "every step of claim 1 of the Asserted Patents when using the Accused Products in the laboratory and sequencing the amplified DNA." Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 76 of the Second Amended Complaint.

77. Paragraph 77 of the Second Amended Complaint contains statements of opinion and legal conclusions to which no response is required. To the extent a response is required, the Defendants deny each and every allegation in paragraph 77 of the Second Amended Complaint.

78. The Defendants aver that ArcherDX, Inc.'s Amended Complaint in *ArcherDX, Inc. v. Qiagen Sciences, LLC*, Case No. 18-1019 MN (D. Del.), D.I. 130, ¶ 20, states, "The

VariantPlex®, FusionPlex®, Reveal ctDNA™, and Immunoverse™ products, including custom kits, are sold as ‘research use only’ products to customers, including researchers clinical laboratories, contract research organizations, and pharmaceutical and biotechnology companies (collectively, ‘End- users’).” Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 78 of the Second Amended Complaint.

79. The Defendants admit that the quoted language appears in ArcherDX, Inc.’s Amended Complaint in *ArcherDX, Inc. v. Qiagen Sciences, LLC*, Case No. 18-1019 MN (D. Del.), D.I. 130, ¶ 20. The Defendants aver that the paragraph refers to the specific products VariantPlex®, FusionPlex®, Reveal ctDNA™, and Immunoverse™, and states, “Archer sells various products within four product lines that utilize AMP technology: VariantPlex®, FusionPlex®, Reveal ctDNA™, and Immunoverse™.” Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 79 of the Second Amended Complaint.

80. The Defendants admit that a document purporting to be a claim chart for the Asserted Patents, and documents cited in the claim chart, are attached to the Second Amended Complaint as Exhibits 6-10 and Exhibits 12-41, respectively. The claim chart contains statements of opinion and legal conclusions to which no response is required. To the extent a response is required, the Defendants specifically deny each and every allegation in the claim chart, and further deny that Exhibits 12-41 support the allegations, opinions, and legal conclusions in the claim chart. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 80 of the Second Amended Complaint.

81. Exhibits 6-10 contains statements of opinion and legal conclusions to which no response is required. To the extent a response is required, the Defendants deny each and every

allegation in Exhibits 6-10. The Defendants further deny each and every allegation in paragraph 81 of the Second Amended Complaint.

82. The allegations of paragraph 82 of the Second Amended Complaint constitute legal conclusions that require no response. The Defendants admit that LIQUIDPlex™ and VariantPlex® are products sold for research use only and use ArcherDX's proprietary AMP™ chemistry. The Defendants further admits that ArcherDX is currently developing its STRATAFIDE™ and PCM products for approval or clearance by the FDA as IVDs. The Defendants further admit that Archer®MET is an IVD product that has been approved in Japan only. The Defendants admit that AMP™ stands for "Anchored Multiplex PCR." The Defendants admit that ArcherDX's technology is utilized to preferentially enrich highly fragmented ctDNA, DNA, or RNA. Except as expressly admitted herein, to the extent a response is required, the Defendants deny each and every allegation in paragraph 82 of the Second Amended Complaint.

83. The allegations of paragraph 83 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent that paragraph 83 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, to the extent a response is required, the Defendants deny each and every allegation in paragraph 83 of the Second Amended Complaint.

84. To the extent that paragraph 84 excerpts the contents of a journal article, the document speaks for itself. The Defendants admit that the product formerly called Reveal ctDNA™ is now called LiquidPlex™. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 84 of the Second Amended Complaint.



85. The allegations of paragraph 85 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent that paragraph 85 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, to the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 85 of the Second Amended Complaint.

86. The allegations of paragraph 86 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent that paragraph 86 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, to the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 86 of the Second Amended Complaint.

87. The allegations of paragraph 87 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent that paragraph 87 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, to the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 87 of the Second Amended Complaint.

88. To the extent that paragraph 88 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 88 of the Second Amended Complaint.

89. The allegations of paragraph 89 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent that paragraph 89 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, to the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 89 of the Second Amended Complaint.

90. The allegations of paragraph 90 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent that paragraph 90 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, to the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 90 of the Second Amended Complaint.

91. The allegations of paragraph 91 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent that paragraph 91 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, to the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 91 of the Second Amended Complaint.

92. To the extent that paragraph 92 excerpts the contents of a journal article, the document speaks for itself. The Defendants are without knowledge or information sufficient to form a belief as to the truth of the remaining allegations, and therefore deny each and every remaining allegation in paragraph 92 of the Second Amended Complaint.

93. To the extent that paragraph 93 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 93 of the Second Amended Complaint.

94. The Defendants deny each and every allegation in paragraph 94 of the Second Amended Complaint.

95. To the extent that paragraph 95 excerpts the contents of a journal article, the document speaks for itself. To the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 95 of the Second Amended Complaint.

96. The allegations of paragraph 96 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 96 of the Second Amended Complaint.

97. The allegations of paragraph 97 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 97 of the Second Amended Complaint.

98. The Defendants admit that the LIQUIDPlex™ technology uses AMP™ chemistry to create target-enriched libraries for next-generation sequencing (NGS). Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 98 of the Second Amended Complaint.

99. To the extent that paragraph 99 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 99 of the Second Amended Complaint.

100. To the extent that paragraph 100 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 100 of the Second Amended Complaint.

101. The Defendants admit that the VariantPlex technology uses AMP™ chemistry to create target-enriched libraries for next-generation sequencing (NGS). Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 101 of the Second Amended Complaint.

102. To the extent that paragraph 102 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 102 of the Second Amended Complaint.

103. To the extent that paragraph 103 excerpts the contents of an ArcherDX document, the document speaks for itself. The Defendants admit that PCM is intended to be a bespoke product—adjusted as needed on a patient-by-patient basis. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 103 of the Second Amended Complaint.

104. The allegations of paragraph 104 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent that paragraph 104 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, to the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 104 of the Second Amended Complaint.

105. To the extent that paragraph 105 excerpts the contents of a journal article, the document speaks for itself. The Defendants are without knowledge or information sufficient to form a belief as to the truth of the remaining allegations, and therefore deny each and every remaining allegation in paragraph 105 of the Second Amended Complaint.

106. To the extent that paragraph 106 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted, the Defendants deny each and every allegation in paragraph 106 of the Second Amended Complaint.

107. To the extent that paragraph 107 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, to the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 107 of the Second Amended Complaint.

108. The Defendants deny each and every allegation in paragraph 108 of the Second Amended Complaint.

109. To the extent that paragraph 109 excerpts the contents of a journal article, the document speaks for itself. Except as expressly admitted herein, to the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 109 of the Second Amended Complaint.

110. The allegations of paragraph 110 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 110 of the Second Amended Complaint.

111. The allegations of paragraph 111 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 111 of the Second Amended Complaint.

112. The allegations of paragraph 112 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent that paragraph 112 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, to the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 112 of the Second Amended Complaint.

113. The allegations of paragraph 113 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 113 of the Second Amended Complaint.

114. To the extent that paragraph 114 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 114 of the Second Amended Complaint.

115. To the extent that paragraph 115 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 115 of the Second Amended Complaint.

116. The allegations of paragraph 116 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent that paragraph 116 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, to the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 116 of the Second Amended Complaint.

117. The allegations of paragraph 117 of the Second Amended Complaint constitute legal conclusions that require no response. Except as expressly admitted herein, to the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 117 of the Second Amended Complaint.

118. ArcherDX admits that LIQUIDPlex™ utilizes ArcherDX's proprietary AMP™ technology. To the extent that paragraph 83 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 118 of the Second Amended Complaint.

119. The Defendants admit that LIQUIDPlex™ and VariantPlex® utilize ArcherDX's proprietary AMP™ technology and have application for solid tumors as well as hematological malignancies. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 119 of the Second Amended Complaint.

120. The Defendants admit that VariantPlex® utilizes ArcherDX's proprietary AMP™ technology. To the extent that paragraph 120 excerpts the contents of an ArcherDX document,

the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 120 of the Second Amended Complaint.

121. The Defendants admit that VariantPlex<sup>®</sup> utilizes ArcherDX's proprietary AMP<sup>™</sup> technology. To the extent that paragraph 121 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 121 of the Second Amended Complaint.

122. The Defendants admit that LIQUIDPlex<sup>™</sup> and VariantPlex<sup>®</sup> are products available for research use only and are not IVDs. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 122 of the Second Amended Complaint.

123. The allegations of paragraph 123 of the Second Amended Complaint constitute legal conclusions that require no response. The Defendants admit that LIQUIDPlex<sup>™</sup> is a product available for research use only and is not an IVD. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 123 of the Second Amended Complaint.

124. The allegations of paragraph 124 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent a response is deemed required, the Defendants specifically deny that they have or have had the requisite intent or knowledge to induce or contribute to the direct infringement of the Asserted Patent by another. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 124 of the Second Amended Complaint.

125. The allegations of paragraph 125 of the Complaint constitute legal conclusions that require no response. The Defendants admit that VariantPlex<sup>®</sup> is a product available for research

use only and is not an IVD. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 125 of the Second Amended Complaint.

126. The allegations of paragraph 126 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent a response is deemed required, the Defendants specifically deny that they have or have had the requisite intent or knowledge to induce or contribute to the direct infringement of the Asserted Patent by another. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 126 of the Second Amended Complaint.

127. The Defendants admit that Archer<sup>®</sup>MET utilizes ArcherDX's proprietary AMP<sup>™</sup> technology. To the extent that paragraph 127 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 127 of the Second Amended Complaint.

128. The Defendants admit that Archer<sup>®</sup>MET has been recently approved in Japan only. Natera's allegations fail to state a claim upon which relief may be granted. For example, paragraph 128 of the Complaint does not plausibly allege that the Defendants have engaged in any activities with respect to Archer<sup>®</sup>MET that would constitute patent infringement under 35 U.S.C. § 271. The Asserted Patent recites only method claims, which cannot, as a matter of law, be infringed by the alleged manufacturing of the Archer<sup>®</sup>MET product in the United States or the alleged exporting of the Archer<sup>®</sup>MET product from the United States. Indeed, the alleged shipment of the Archer<sup>®</sup>MET product overseas cannot constitute infringement "as Section 271(f) does not encompass devices that may be used to practice a patented method." *Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc.*, 576 F.3d 1348, 1365 (Fed. Cir. 2009) (en banc).



Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 128 of the Second Amended Complaint.

129. To the extent that paragraph 129 excerpts the contents of an ArcherDX document, the document speaks for itself. Natera's allegations fail to state a claim upon which relief may be granted. For example, paragraph 129 of the Second Amended Complaint does not plausibly allege that the Defendants have engaged in any activities with respect to Archer<sup>®</sup>MET that would constitute patent infringement under 35 U.S.C. § 271. The Asserted Patent recites only method claims, which cannot, as a matter of law, be infringed by the alleged manufacturing of the Archer<sup>®</sup>MET product in the United States or the alleged exporting of the Archer<sup>®</sup>MET product from the United States. Indeed, the alleged shipment of the Archer<sup>®</sup>MET product overseas cannot constitute infringement "as Section 271(f) does not encompass devices that may be used to practice a patented method." *Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc.*, 576 F.3d 1348, 1365 (Fed. Cir. 2009) (en banc). Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 129 of the Second Amended Complaint.

130. To the extent that paragraph 130 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 130 of the Second Amended Complaint.

131. The allegations of paragraph 131 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent a response is deemed required, the Defendants specifically deny that they performed in the United States any claimed method of the Asserted Patents. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 131 of the Second Amended Complaint.

132. The Defendants aver that ArcherDX is currently developing its STRATAFIDE™ IVD product for approval or clearance by the FDA. To the extent that paragraph 132 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 132 of the Second Amended Complaint.

133. The Defendants aver that ArcherDX is currently developing its PCM IVD product for approval or clearance by the FDA. The Defendants aver that PCM is intended to be a bespoke product—adjusted as needed on a patient-by-patient basis. To the extent paragraph 133 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 133 of the Second Amended Complaint.

134. To the extent paragraph 134 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 134 of the Second Amended Complaint.

135. To the extent paragraph 135 excerpts the contents of ArcherDX documents, those documents speak for themselves. The Defendants aver that STRATAFIDE and PCM are in development as IVDs. As FDA guidance explains, one type of RUO “is an IVD product that is in the laboratory research phase of development.” *Natera, Inc. v. ArcherDX, Inc.*, Case No. 20-cv-1047-LPS (D. Del.), D.I. 1, Ex. 21 at 7. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 135 of the Second Amended Complaint. Natera’s allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of

a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Archer cannot commercialize any IVD product without first obtaining FDA approval. Indeed, Natera fails to allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1).

136. The allegations of paragraph 136 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent a response is deemed required, the Defendants deny each and every allegation in paragraph 136 of the Second Amended Complaint. The Defendants specifically deny that they have engaged in activities with respect to STRATAFIDE and PCM not reasonably related to FDA approval. Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Archer cannot commercialize any IVD product without first obtaining FDA approval. Indeed, Natera fails to allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1).

137. The Defendants deny each and every allegation in paragraph 137 of the Second Amended Complaint. As FDA guidance explains, one type of RUO "is an IVD product that is in the laboratory research phase of development." *Natera, Inc. v. ArcherDX, Inc.*, Case No. 20-cv-1047-LPS (D. Del.), D.I. 1, Ex. 21 at 7. Uses of products in development as IVDs that require FDA approval are within 35 U.S.C. 271(e)(1)'s safe harbor. *See Eli Lilly & Co v. Medtronic*,

*Inc.*, 496 U.S. 661 (1990). Natera’s allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. The Defendants cannot commercialize any IVD product without first obtaining FDA approval. Indeed, Natera fails to plausibly allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1).

138. The allegations of paragraph 138 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent that paragraph 138 refers to the contents of an ArcherDX document, the document speaks for itself. The Defendants aver that the TRACERx investigators, led by Professor Charles Swanton, Group Leader, University College London (“UCL”) and the Francis Crick Institute, and Dr. Christopher Abbosh, Principal Clinical Fellow, UCL, are utilizing ArcherDX’s technology—and not Natera’s inferior technology—to detect low-volume minimal residual disease at high levels of sensitivity to help achieve TRACERx’s goal of a more personalized approach to developing cancer treatments. Natera’s allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. The Defendants cannot commercialize any IVD product without first obtaining FDA approval.

Indeed, Natera fails to plausibly allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 138 of the Second Amended Complaint.

139. The allegations of paragraph 139 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent that paragraph 139 refers to the contents of an ArcherDX document, the document speaks for itself. Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Archer cannot commercialize any IVD product without first obtaining FDA approval. Indeed, Natera fails to plausibly allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 139 of the Second Amended Complaint.

140. The allegations of paragraph 140 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent that paragraph 140 refers to the contents of an ArcherDX document, the document speaks for itself. The Defendants aver that Exhibit 17 to the Second Amended Complaint states that PCM is "currently an investigational device." Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim

of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Archer cannot commercialize any IVD product without first obtaining FDA approval. Indeed, Natera fails to plausibly allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 140 of the Second Amended Complaint.

141. The allegations of paragraph 141 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent that paragraph 141 refers to the contents of an ArcherDX document, the document speaks for itself. The Defendants aver that Exhibit 26 to the Second Amended Complaint states, “The assays are currently for investigational use only.” Natera’s allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. ArcherDX cannot commercialize any IVD product without first obtaining FDA approval. Indeed, Natera fails to plausibly allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 141 of the Second Amended Complaint.

142. The allegations of paragraph 142 of the Second Amended Complaint constitute legal conclusions that require no response. Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Archer cannot commercialize any IVD product without first obtaining FDA approval. Indeed, Natera fails to plausibly allege that the Defendants have engaged in any activities with respect to STRATAFIDE<sup>TM</sup> or PCM that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). The Defendants deny each and every allegation in paragraph 142 of the Second Amended Complaint.

143. The allegations of paragraph 143 of the Second Amended Complaint constitute legal conclusions that require no response. Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Archer cannot commercialize any IVD product without first obtaining FDA approval. Indeed, Natera fails to plausibly allege that the Defendants have engaged in any activities with respect to STRATAFIDE<sup>TM</sup> or PCM that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 143 of the Second Amended Complaint.

144. To the extent that paragraph 144 excerpts the contents of an ArcherDX document, the document speaks for itself. ArcherDX specifically denies that it “received [any] financing as a result of its infringing use of Natera’s patented technology.” Natera’s allegation that ArcherDX “announced the close of a \$55 million Series C financing round, the proceeds of which are intended to be used to support the launch of Stratafide and PCM” (emphasis added) fails to give rise to a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. The Defendants cannot commercialize any IVD product without first obtaining FDA approval. Moreover, Natera also fails to plausibly allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 144 of the Second Amended Complaint.

145. To the extent that paragraph 145 excerpts the contents of an ArcherDX document, the document speaks for itself. The Defendants specifically deny that they “ha[ve] commercially benefited and will benefit from the infringing use of PCM and STRATAFIDE by others.” Natera fails to allege how the alleged licensing activities constitute a commercial sale or offer for sale. Natera’s allegations that ArcherDX “anticipated that Stratafide *would be the first IVD* to be marketed under the partnership between [ArcherDX] and Illumina” and that ArcherDX “announced that it *planned to launch PCM for diagnostic use* as part of this commercial partnership” (emphasis added) fail to give rise to a case or controversy between the parties under



Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. The Defendants cannot commercialize any IVD product without first obtaining FDA approval. Indeed, Natera fails to plausibly allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 145 of the Second Amended Complaint.

146. The Defendants aver that the TRACERx investigators, led by Professor Charles Swanton, Group Leader, University College London (“UCL”) and the Francis Crick Institute, and Dr. Christopher Abbosh, Principal Clinical Fellow, UCL, are utilizing ArcherDX’s technology—and not Natera’s inferior technology—to detect low-volume minimal residual disease at high levels of sensitivity to help achieve TRACERx’s goal of a more personalized approach to developing cancer treatments. Natera’s allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. The Defendants cannot commercialize any IVD product without first obtaining FDA approval. Indeed, Natera fails to plausibly allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Natera’s allegations further fail to state a claim upon

which relief may be granted. Paragraph 146 of the Second Amended Complaint does not plausibly allege that the Defendants have engaged in any activities with respect to the TRACERx study that would constitute patent infringement under 35 U.S.C. § 271. The Asserted Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting those components (e.g., kits) from the United States. Exporting components (e.g., kits) overseas cannot constitute infringement of method claims “as Section 271(f) does not encompass devices that may be used to practice a patented method.” *Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc.*, 576 F.3d 1348, 1365 (Fed. Cir. 2009) (en banc). Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 146 of the Second Amended Complaint.

147. The Defendants admit that ArcherDX received the FDA’s Breakthrough Device Designation for STRATAFIDE™ in December 2018. Natera’s allegation that ArcherDX “intends to sell the product for diagnostic use immediately upon approval” (emphasis added) fails to give rise to a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. The Defendants cannot commercialize any IVD product without first obtaining FDA approval. Paragraph 147 of the Second Amended Complaint further fails to plausibly allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 147 of the Second Amended Complaint.

148. The Defendants admit that ArcherDX received the FDA’s Breakthrough Device Designation for PCM in January 2020. Natera’s allegation that ArcherDX “intends to sell the product for diagnostic use immediately upon approval” (emphasis added) fails to give rise to a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. The Defendants cannot commercialize any IVD product without first obtaining FDA approval. Paragraph 148 of the Second Amended Complaint further fails to plausibly allege that the Defendants have engaged in any activities with respect to PCM that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 148 of the Second Amended Complaint.

149. The allegations of paragraph 149 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent a response is deemed required, the Defendants specifically deny that they have or have had the requisite intent or knowledge to induce or contribute to the direct infringement of the Asserted Patent by another. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 149 of the Second Amended Complaint.

150. The allegations of paragraph 150 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent a response is deemed required, the Defendants specifically deny that they have or have had the requisite intent or knowledge to induce or contribute to the direct infringement of the Asserted Patent by another. Except as expressly

admitted herein, the Defendants deny each and every allegation in paragraph 150 of the Second Amended Complaint.

151. The Defendants deny each and every allegation in paragraph 151 of the Second Amended Complaint. ArcherDX avers that it developed its own proprietary AMP<sup>TM</sup> chemistry, technology platform, and applications.

152. To the extent that paragraph 152 excerpts the contents of an ArcherDX document, the document speaks for itself. The Defendants aver that the TRACERx investigators, led by Professor Charles Swanton, Group Leader, UCL and the Francis Crick Institute, and Dr. Christopher Abbosh, Principal Clinical Fellow, UCL, are utilizing ArcherDX's technology—and not Natera's inferior technology—to detect low-volume minimal residual disease at high levels of sensitivity to help achieve TRACERx's goal of a more personalized approach to developing cancer treatments. Paragraph 152 of the Second Amended Complaint further contains legal conclusions that require no response. To the extent paragraph 152 contains factual allegations, the Defendants are without knowledge or information sufficient to form a belief as to the truth of those allegations, and therefore deny each and every allegation in that paragraph.

153. The Defendants deny each and every allegation in paragraph 153 of the Second Amended Complaint. ArcherDX avers that it developed its own proprietary AMP<sup>TM</sup> chemistry, technology platform, and applications.

154. The Defendants admit that LIQUIDPlex<sup>TM</sup>, VariantPlex<sup>®</sup>, and FusionPlex<sup>®</sup> utilize ArcherDX's proprietary AMP<sup>TM</sup> technology to preferentially enrich highly fragmented ctDNA, DNA, or RNA and have application for solid tumors as well as hematological malignancies. LIQUIDPlex<sup>TM</sup>, VariantPlex<sup>®</sup>, and FusionPlex<sup>®</sup> are products available for research use only (as

opposed to IVDs). Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 154 of the Second Amended Complaint.

155. The Defendants admit that FusionPlex<sup>®</sup> is a product available for research use only, and not for the diagnosis or treatment of disease; FusionPlex<sup>®</sup> is not an IVD. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 155 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities with respect to STRATAFIDE<sup>™</sup> or PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Indeed, the Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities in the U.S. with respect to Archer<sup>®</sup>MET (or any other oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '482 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE<sup>™</sup>, PCM, or Archer<sup>®</sup>MET (or any other oncology product in development or any other oncology product that is used overseas, and that utilizes the same technology as any of the Accused Products). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a

claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

156. The allegations of paragraph 156 of the Second Amended Complaint constitute legal conclusions that require no response. To the extent a response is deemed required, the Defendants specifically deny that they have or have had the requisite intent or knowledge to induce or contribute to the direct infringement of any Asserted Patent by another. The Defendants deny each and every other allegation of paragraph 156 of the Second Amended Complaint.

157. To the extent that paragraph 157 recites an ArcherDX document, the document speaks for itself. The Defendants are without knowledge or information sufficient to form a belief as to how Natera monetizes its technology and, on that basis, deny that Natera is a “direct competitor.” Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 157 of the Second Amended Complaint.

158. Archer admits that it gained knowledge of the ’814 Patent after it received a copy of the initial complaint in this action. Invitae admits that it gained knowledge of the ’814 Patent at least as early of the date of the Second Amended Complaint. Except as expressly admitted herein, the Defendants denies each and every allegation of paragraph 158 of the Second Amended Complaint.

159. Archer has knowledge of the ’172 patent at least as early as the date of this first amended complaint in this action. Invitae admits that it gained knowledge of the ’172 Patent at least as early of the date of the Second Amended Complaint.

160. Archer has knowledge of the ’482 patent at least as early as the date of this first amended complaint in this action. Invitae admits that it gained knowledge of the ’482 Patent at least as early of the date of the Second Amended Complaint.

161. Archer has knowledge of the '708 patent at least as early as the date of this first amended complaint in this action. Invitae admits that it gained knowledge of the '708 Patent at least as early of the date of the Second Amended Complaint.

162. Archer has knowledge of the '220 patent at least as early as the date of the complaint in *Natera, Inc. v. ArcherDX, Inc.*, Case No. 20-cv-1047-LPS (D. Del.). Invitae admits that it gained knowledge of the '220 Patent at least as early of the date of the Second Amended Complaint.

163. The Defendants admit to knowledge of the Asserted Patents at least as early as the dates set forth in ¶¶ 158-62. The Defendants specifically deny the alleged infringing activities. To the extent paragraph 163 contains factual allegations, Defendants neither admit nor deny the substance of those allegations and assert the attorney-client privilege and work product protections.

#### **RESPONSE TO COUNT I: ALLEGED INFRINGEMENT OF THE '814 PATENT**

164. The Defendants restate and incorporate by reference, their preliminary statement, and each and every response set forth above in paragraphs 1-163 of its Answer, as if fully set forth herein.

165. The Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 165 of the Second Amended Complaint, and therefore deny each and every allegation in that paragraph.

166. The Defendants deny each and every allegation of paragraph 166 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1).

Moreover, the Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities in the U.S. with respect to Archer<sup>®</sup>MET (or any other oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '814 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE<sup>™</sup>, PCM, or Archer<sup>®</sup>MET (or any other oncology product in development or used overseas, and that utilizes the same technology as any of the Accused Products). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

167. The Defendants deny each and every allegation of paragraph 167 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities with respect to STRATAFIDE<sup>™</sup> or PCM (or any other IVD oncology product in development that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Indeed, the Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities in the U.S. with respect to Archer<sup>®</sup>MET (or any other



oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '814 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE™, PCM, or Archer®MET (or any other oncology product in development or any other oncology product used overseas, and that utilizes the same technology as any of the Accused Products). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

168. The Defendants deny each and every allegation of paragraph 168 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Indeed, the Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities in the U.S. with respect to Archer®MET (or any other oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '814 Patent

recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE™, PCM, or Archer®MET (or any other oncology product in development or used overseas, and that utilizes the same technology as any of the Accused Products). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

169. The Defendants deny each and every allegation of paragraph 169 of the Second Amended Complaint.

170. The Defendants deny each and every allegation of paragraph 170 of the Second Amended Complaint.

**RESPONSE TO COUNT II: REQUEST FOR DECLARATORY JUDGMENT  
RELATING TO ALLEGED FUTURE INFRINGEMENT OF THE '814 PATENT**

171. The Defendants restate and incorporate by reference, its preliminary statement, and each and every response set forth above in paragraphs 1-170 of its Answer, as if fully set forth herein.

172. The Defendants admit that ArcherDX has received the FDA's Breakthrough Device Designation for STRATAFIDE™ and PCM. The Defendants deny that they have sought or received, or presently intends to seek, Breakthrough Device Designation for LIQUIDPlex™ from the FDA. Natera's allegation that ArcherDX "intends to engage in the commercial manufacture, use, offer for sale, and sale of the Accused Products *if* and when it receives FDA approval to do so" (emphasis added) fails to give rise to a case or controversy between the parties under Article

III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 172 of the Second Amended Complaint.

173. The Second Amended Complaint fails to plead facts supporting “[a]n actual, substantial, and justiciable controversy” with respect to at least STRATAFIDE™, PCM, and Archer®MET (and any other oncology products in development or any other oncology product used overseas, and that utilizes the same technology as any of the Accused Products). Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 173 of the Second Amended Complaint.

174. The Defendants deny each and every allegation of paragraph 174 of the Second Amended Complaint.

175. The Defendants deny each and every allegation of paragraph 175 of the Second Amended Complaint.

176. The Defendants deny each and every allegation of paragraph 176 of the Second Amended Complaint.

**RESPONSE TO COUNT III: ALLEGED INFRINGEMENT OF THE '172 PATENT**

177. The Defendants restate and incorporate by reference, its preliminary statement, and each and every response set forth above in paragraphs 1-176 of its Answer, as if fully set forth herein.

178. The Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 178 of the Second Amended Complaint, and therefore deny each and every allegation in that paragraph.

179. The Defendants deny each and every allegation of paragraph 179 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Indeed, the Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities in the U.S. with respect to Archer®MET (or any other oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '172 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE™, PCM, or Archer®MET (or any other oncology product in development or any other oncology product used overseas, and that utilizes the same technology as any of the Accused Products). In particular,

Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

180. The Defendants deny each and every allegation of paragraph 180 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Indeed, the Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities in the U.S. with respect to Archer®MET (or any other oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '172 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE™, PCM, or Archer®MET (or any other oncology product in development or any other oncology product used overseas, and that utilizes the same technology as any of the Accused Products). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim

that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

181. The Defendants deny each and every allegation of paragraph 181 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Indeed, the Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities in the U.S. with respect to Archer®MET (or any other oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '172 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE™, PCM, or Archer®MET (or any other oncology product in development or any other oncology product used overseas, and that utilizes the same technology as any of the Accused Products). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

182. The Defendants deny each and every allegation of paragraph 182 of the Second Amended Complaint.

183. The Defendants deny each and every allegation of paragraph 183 of the Second Amended Complaint.

**RESPONSE TO COUNT IV: REQUEST FOR DECLARATORY JUDGMENT  
RELATING TO ALLEGED FUTURE INFRINGEMENT OF THE '172 PATENT**

184. The Defendants restate and incorporate by reference, its preliminary statement, and each and every response set forth above in paragraphs 1-183 of its Answer, as if fully set forth herein.

185. The Defendants admit that ArcherDX has received the FDA's Breakthrough Device Designation for STRATAFIDE™ and PCM. The Defendants deny that they have sought or received, or presently intends to seek, Breakthrough Device Designation for LIQUIDPlex™ from the FDA. Natera's allegation that ArcherDX "intends to engage in the commercial manufacture, use, offer for sale, and sale of the Accused Products if and when it receives FDA approval to do so" (emphasis added) fails to give rise to a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 185 of the Second Amended Complaint.

186. The Second Amended Complaint fails to plead facts supporting "[a]n actual, substantial, and justiciable controversy" with respect to at least STRATAFIDE™, PCM, and Archer®MET (or any other oncology product in development or any other oncology product used

overseas, and that utilizes the same technology as any of the Accused Products). Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 186 of the Second Amended Complaint.

187. The Defendants deny each and every allegation of paragraph 187 of the Second Amended Complaint.

188. The Defendants deny each and every allegation of paragraph 188 of the Second Amended Complaint.

189. The Defendants deny each and every allegation of paragraph 189 of the Second Amended Complaint.

#### **RESPONSE TO COUNT V: ALLEGED INFRINGEMENT OF THE '482 PATENT**

190. The Defendants restate and incorporate by reference, its preliminary statement, and each and every response set forth above in paragraphs 1-189 of its Answer, as if fully set forth herein.

191. The Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 191 of the Second Amended Complaint, and therefore deny each and every allegation in that paragraph.

192. The Defendants deny each and every allegation of paragraph 192 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM (or any other IVD oncology product in development and that utilizes the same technology



as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Indeed, the Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities in the U.S. with respect to Archer®MET (or any other oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '482 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE™, PCM, or Archer®MET (or any other oncology product in development or any other oncology product used overseas, and that utilizes the same technology as any of the Accused Products). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

193. The Defendants deny each and every allegation of paragraph 193 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Indeed, the Defendants cannot commercialize any IVD product without first obtaining FDA

approval. As another example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities in the U.S. with respect to Archer<sup>®</sup>MET (or any other oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '482 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE<sup>™</sup>, PCM, or Archer<sup>®</sup>MET (or any other oncology product in development or any other oncology product used overseas, and that utilizes the same technology as any of the Accused Products). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

194. The Defendants deny each and every allegation of paragraph 194 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities with respect to STRATAFIDE<sup>™</sup> or PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Indeed, the Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities in the U.S. with respect to Archer<sup>®</sup>MET (or any other

oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '482 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE™, PCM, or Archer®MET (or any other oncology product in development or any other oncology product that is used overseas, and that utilizes the same technology as any of the Accused Products). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

195. The Defendants deny each and every allegation of paragraph 195 of the Second Amended Complaint.

196. The Defendants deny each and every allegation of paragraph 196 of the Second Amended Complaint.

**RESPONSE TO COUNT VI: REQUEST FOR DECLARATORY JUDGMENT  
RELATING TO ALLEGED FUTURE INFRINGEMENT OF THE '482 PATENT**

197. The Defendants restate and incorporate by reference, its preliminary statement, and each and every response set forth above in paragraphs 1-196 of its Answer, as if fully set forth herein.

198. The Defendants admit that ArcherDX has received the FDA's Breakthrough Device Designation for STRATAFIDE™ and PCM. The Defendants deny that they have sought or received, or presently intends to seek, Breakthrough Device Designation for LIQUIDPlex™ from

the FDA. Natera's allegation that ArcherDX "intends to engage in the commercial manufacture, use, offer for sale, and sale of the Accused Products if and when it receives FDA approval to do so" fails to give rise to a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 198 of the Second Amended Complaint.

199. The Second Amended Complaint fails to plead facts supporting "[a]n actual, substantial, and justiciable controversy" with respect to at least STRATAFIDE™, PCM, and Archer®MET (or any other oncology product in development or any other oncology product used overseas, and that utilizes the same technology as any of the Accused Products). Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 199 of the Second Amended Complaint.

200. The Defendants deny each and every allegation of paragraph 200 of the Second Amended Complaint.

201. The Defendants deny each and every allegation of paragraph 201 of the Second Amended Complaint.

202. The Defendants deny each and every allegation of paragraph 202 of the Second Amended Complaint.

**RESPONSE TO COUNT VII: ALLEGED INFRINGEMENT OF THE '708 PATENT**

203. The Defendants restate and incorporate by reference, its preliminary statement, and each and every response set forth above in paragraphs 1-202 of its Answer, as if fully set forth herein.

204. The Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 204 of the Second Amended Complaint, and therefore deny each and every allegation in that paragraph.

205. The Defendants deny each and every allegation of paragraph 205 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Indeed, the Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities in the U.S. with respect to Archer® MET (or any other oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '708 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE™, PCM, or

Archer<sup>®</sup>MET (or any other oncology product in development or any other oncology product used overseas, and that utilizes the same technology as any of the Accused Products). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

206. The Defendants deny each and every allegation of paragraph 206 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities with respect to STRATAFIDE<sup>™</sup> or PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Indeed, the Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities in the U.S. with respect to Archer<sup>®</sup>MET (or any other oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '708 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE<sup>™</sup>, PCM, or Archer<sup>®</sup>MET (or any other oncology product in development or any other oncology product used overseas, and that utilizes the same technology as any of the Accused Products). In particular,

Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

207. The Defendants deny each and every allegation of paragraph 207 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Indeed, the Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not allege that the Defendants have engaged in any activities in the U.S. with respect to Archer®MET (or any other oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '708 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE™, PCM, or Archer®MET (or any other oncology product in development or any other oncology product used overseas, and that utilizes the same technology as any of the Accused Products). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a

claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

208. The Defendants deny each and every allegation of paragraph 208 of the Second Amended Complaint.

209. The Defendants deny each and every allegation of paragraph 209 of the Second Amended Complaint.

**RESPONSE TO COUNT VIII: REQUEST FOR DECLARATORY JUDGMENT  
RELATING TO ALLEGED FUTURE INFRINGEMENT OF THE '708 PATENT**

210. The Defendants restate and incorporate by reference, its preliminary statement, and each and every response set forth above in paragraphs 1-209 of its Answer, as if fully set forth herein.

211. The Defendants admit that they have received the FDA's Breakthrough Device Designation for STRATAFIDE<sup>TM</sup> and PCM. The Defendants deny that they have sought or received, or presently intends to seek, Breakthrough Device Designation for LIQUIDPlex<sup>TM</sup>, FusionPlex<sup>®</sup>, or VariantPlex<sup>®</sup> from the FDA. Natera's allegation that ArcherDX "intends to engage in the commercial manufacture, use, offer for sale, and sale of the Accused Products if and when it receives FDA approval to do so" (emphasis added) fails to give rise to a case or controversy between the parties under Article III of the Constitution and the Declaratory Judgment Act. Indeed, The Defendants cannot commercialize any IVD product without first obtaining FDA approval. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 211 of the Second Amended Complaint.



212. The Second Amended Complaint fails to plead facts supporting “[a]n actual, substantial, and justiciable controversy” with respect to at least STRATAFIDE™, PCM, and Archer®MET (or any other oncology product in development or any other oncology product used overseas, and that utilizes the same technology as any of the Accused Products). Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Except as expressly admitted herein, the Defendants deny each and every allegation of paragraph 212 of the Second Amended Complaint.

213. The Defendants deny each and every allegation of paragraph 213 of the Second Amended Complaint.

214. The Defendants deny each and every allegation of paragraph 214 of the Second Amended Complaint.

215. The Defendants deny each and every allegation of paragraph 215 of the Second Amended Complaint.

#### **RESPONSE TO COUNT IX: ALLEGED INFRINGEMENT OF THE '220 PATENT**

216. The Defendants restate and incorporate by reference, its preliminary statement, and each and every response set forth above in paragraphs 1-215 of its Answer, as if fully set forth herein.

217. The Defendants deny each and every allegation in paragraph 217 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not plausibly allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM (or any other IVD oncology product in development and that utilizes

the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). The Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not plausibly allege that the Defendants have engaged in any activities in the U.S. with respect to Archer<sup>®</sup>MET (or any other oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '220 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE<sup>™</sup>, PCM, or Archer<sup>®</sup>MET (or any other oncology product in development or used overseas, and that utilizes the same technology as any of the Accused Products). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

218. The Defendants deny each and every allegation in paragraph 218 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not plausibly allege that the Defendants have engaged in any activities with respect to STRATAFIDE<sup>™</sup> or PCM (or any other IVD oncology product in development that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). The Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not

plausibly allege that the Defendants have engaged in any activities in the U.S. with respect to Archer<sup>®</sup>MET (or any other oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '220 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE<sup>™</sup>, PCM, or Archer<sup>®</sup>MET (or any other oncology product in development or any other oncology product used overseas, and that utilizes the same technology as any of the Accused Products). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

219. The Defendants deny each and every allegation in paragraph 219 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not plausibly allege that the Defendants have engaged in any activities with respect to STRATAFIDE<sup>™</sup> or PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). The Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not plausibly allege that the Defendants have engaged in any activities in the U.S. with respect to Archer<sup>®</sup>MET (or any other oncology product used overseas and that utilizes the same technology

as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '220 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE™, PCM, or Archer®MET (or any other oncology product in development or used overseas, and that utilizes the same technology as any of the Accused Products). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

220. The Defendants deny each and every allegation in paragraph 220 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not plausibly allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). The Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not plausibly allege that the Defendants have engaged in any activities in the U.S. with respect to Archer®MET (or any other oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '220 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (e.g., kits) in the United States or exporting components (e.g., kits)

from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE™, PCM, or Archer®MET (or any other oncology product in development or used overseas, and that utilizes the same technology as any of the Accused Products). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

221. The Defendants deny each and every allegation in paragraph 221 of the Second Amended Complaint.

222. The Defendants deny each and every allegation in paragraph 222 of the Second Amended Complaint.

**RESPONSE TO COUNT X: REQUEST FOR DECLARATORY JUDGMENT  
RELATING TO ALLEGED FUTURE INFRINGEMENT OF THE '220 PATENT**

223. The Defendants restate and incorporate by reference, its preliminary statement, and each and every response set forth above in paragraphs 1-222 of its Answer, as if fully set forth herein.

224. The Defendants deny each and every allegation in paragraph 224 of the Second Amended Complaint. In addition, the Second Amended Complaint, in whole or in part, fails to state a claim upon which relief may be granted. For example, the Second Amended Complaint does not plausibly allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). The Defendants cannot commercialize any IVD product without first obtaining FDA approval. As another example, the Second Amended Complaint does not

plausibly allege that the Defendants have engaged in any activities in the U.S. with respect to Archer<sup>®</sup>MET (or any other oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The '220 Patent recites only method claims, which cannot, as a matter of law, be infringed by manufacturing components (*e.g.*, kits) in the United States or exporting components (*e.g.*, kits) from the United States. In addition, Natera's allegations fail to give rise to a case or controversy between the parties under Article III of the Constitution with respect to STRATAFIDE<sup>™</sup>, PCM, or Archer<sup>®</sup>MET (or any other oncology product in development or used overseas, and that utilizes the same technology as any of the Accused Products). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

225. The Defendants admit that they have received the FDA's Breakthrough Device Designation for STRATAFIDE<sup>™</sup> and PCM. Natera's allegation that ArcherDX "intends to engage in the commercial manufacture, use, offer for sale, and sale of the Accused Products if and when it receives FDA approval to do so" (emphasis added) fails to give rise to a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act. In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 225 of the Second Amended Complaint.

226. To the extent that paragraph 226 excerpts the contents of an ArcherDX document, the document speaks for itself. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 226 of the Second Amended Complaint.

227. The Second Amended Complaint fails to plausibly allege facts supporting “[a]n actual, substantial, and justiciable controversy” with respect to at least STRATAFIDE™, PCM, and Archer®MET (and any other oncology products in development or any other oncology product used overseas, and that utilizes the same technology as any of the Accused Products). Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 227 of the Second Amended Complaint.

228. The Second Amended Complaint fails to plausibly allege facts supporting an “immediate” controversy with respect to at least STRATAFIDE™, PCM, and Archer®MET (and any other oncology products in development or any other oncology product used overseas, and that utilizes the same technology as any of the Accused Products). To the extent that paragraph 228 excerpts the contents of an ArcherDX document, the document speaks for itself. Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 228 of the Second Amended Complaint.

229. To the extent that paragraph 229 excerpts the contents of an ArcherDX document, the document speaks for itself. Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 229 of the Second Amended Complaint.

230. To the extent that paragraph 230 excerpts the contents of an ArcherDX document, the document speaks for itself. Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 230 of the Second Amended Complaint.

231. The Second Amended Complaint fails to plausibly allege facts supporting a “real” controversy with respect to at least STRATAFIDE™, PCM, and Archer®MET (and any other oncology products in development or any other oncology product used overseas, and that utilizes the same technology as any of the Accused Products). Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all. Except as expressly admitted herein, the Defendants deny each and every allegation in paragraph 231 of the Second Amended Complaint.



232. The Defendants deny each and every allegation in paragraph 232 of the Second Amended Complaint.

233. The Defendants deny each and every allegation in paragraph 233 of the Second Amended Complaint.

234. The Defendants deny each and every allegation in paragraph 234 of the Second Amended Complaint.

### **RESPONSE TO NATERA'S PRAYER FOR RELIEF**

235. The Defendants deny that Natera is entitled to any relief from the Defendants, including the relief Natera seeks in Paragraphs (1)–(6) of its Prayer for Relief. Natera's Prayer for Relief should be denied in its entirety and with prejudice, and Natera should be awarded nothing. The Defendants further deny each and every allegation in Natera's Prayer for Relief.

### **ARCHERDX'S DEFENSES**

236. The Defendants allege and assert the following defenses in response to the allegations in the Second Amended Complaint, undertaking the burden of proof only as to those defenses deemed affirmative defenses by law, regardless of how such defenses are denominated herein. The Defendants reserve the right to amend its Answer, including to modify, amend, and/or expand upon its defenses once discovery progresses. Without conceding that any of the following defenses must necessarily be pled, or that any of the following defenses is not already at issue by virtue of the foregoing denials, and without reducing or removing Natera's burdens of proof on its affirmative claims against the Defendants, the Defendants allege and assert as follows:

#### **FIRST DEFENSE (Failure to State a Claim)**

237. The allegations and claims in the Second Amended Complaint, in whole or in part, fail to state a claim upon which relief may be granted.

238. The Second Amended Complaint fails to plead any specific instances of infringement by the use of any Accused Products. It pleads only that Archer's AMP process "can" perform a claimed method step. *See, e.g.*, D.I. 17, ¶¶ 58-97. However, none of the claims of the Asserted Patents require merely the capacity to perform a certain step. Accordingly, the Second Amended Complaint fails to plead that any Accused Products was actually used in an infringing manner. *See Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1329 (Fed. Cir. 2010).

239. The Second Amended Complaint also does not allege that the Defendants have engaged in any activities with respect to STRATAFIDE™ or PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products) that fall outside the safe harbor provided by 35 U.S.C. § 271(e)(1). Indeed, the Defendants cannot commercialize any IVD product without first obtaining FDA approval.

240. Furthermore, the Second Amended Complaint does not allege that the Defendants have engaged in any activities in the U.S. with respect to Archer®MET (or any other oncology product used overseas and that utilizes the same technology as any of the Accused Products) that would constitute patent infringement under 35 U.S.C. § 271. The Asserted Patents recite only method claims, which cannot, as a matter of law, be infringed by the alleged manufacturing of the Archer®MET product, or any other product, in the United States or the alleged exportation from the United States of the Archer®MET, or any other, product. Indeed, the alleged shipment of the Archer®MET product, or any other product, overseas cannot constitute infringement "as Section 271(f) does not encompass devices that may be used to practice a patented method." *Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc.*, 576 F.3d 1348, 1365 (Fed. Cir. 2009) (en banc).

241. The Second Amended Complaint further fails to state a claim upon which relief may be granted because, as set forth in the Defendants' Counterclaims, the claims of the Asserted Patents are invalid under one or more of 35 U.S.C. § 101, 102, 103, 112, et seq.

**SECOND DEFENSE**  
**(Lack of Subject Matter Jurisdiction)**

242. There is no subject matter jurisdiction because the Second Amended Complaint fails to plead a case or controversy between the parties under Article III of the Constitution or the Declaratory Judgment Act, 28 U.S.C. § 2201 et seq. with respect to ArcherDX's IVD products (including any oncology product in development or any oncology product used overseas). In particular, Natera fails to plead a claim of sufficient immediacy and reality to give rise to Article III jurisdiction or to warrant the issuance of a declaratory judgment. Natera also fails to plead a claim that is ripe for adjudication as it rests upon contingent or future events that may not occur as anticipated, or may not occur at all.

243. None of the Accused Products are presently cleared or approved by the FDA. The Defendants have not sought or received, nor does it presently intend to seek, Breakthrough Device Designation or premarket approval or approval or clearance pursuant to 21 U.S.C. § 360(k) ("510k approval or clearance") from the FDA for LIQUIDPlex™, FusionPlex®, VariantPlex®, or Archer®MET. Archer®MET has been approved, and is only sold in, Japan. LIQUIDPlex™, FusionPlex®, and VariantPlex® are sold in the U.S. as research use only (or "RUO") products, which in contrast to IVD products, do not require FDA approval prior to commercialization. Indeed, both STRATAFIDE™ and PCM, which are IVD products, require premarket approval or 510k approval or clearance to be sold commercially. The Defendants have not, however, even submitted an application for FDA clearance or approval to the FDA for either STRATAFIDE™ or PCM.

244. The development of the data necessary to obtain regulatory clearance and/or approval of STRATAFIDE™ and PCM is ongoing, but is time-consuming and carries with it the risk of not yielding the desired results. Ultimately, the Defendants may not be able to obtain FDA clearance or approval of STRATAFIDE™ or PCM (or, in fact, any other IVD product).

245. PCM is intended to be a bespoke IVD product, and even if FDA approved, the composition and reaction conditions of the product that will be utilized is not presently known—the components will be developed on a patient-by-patient basis.

### **THIRD DEFENSE (Non-Infringement)**

246. The Defendants have not infringed, and are not infringing, literally or under the doctrine of equivalents, directly, or jointly, any valid and enforceable claim of any Asserted Patent.

247. For example, claim 1 of the '814 Patent recites “performing a first PCR...using a universal primer” and “performing a second, nested PCR...using the universal primer and at least 10 inner target-specific primers..., wherein at least one of the primers comprises a sequencing tag.” ArcherDX’s accused AMP™ process does not include “a second, nested PCR... using the universal primer” of the first PCR, nor does “at least one of the [universal primer and at least 10 inner target-specific primers] comprises a sequencing tag.”

248. As another example, claim 1 of the '172 Patent recites “performing a first PCR...using a universal primer” and “performing a second, nested PCR...using the universal primer.” ArcherDX’s accused AMP™ process does not include “a second, nested PCR... using the universal primer” of the first PCR.

249. As another example, claim 1 of the '482 Patent recites “performing a first PCR...using a universal primer” and “performing a second, nested PCR...using the universal

primer.” ArcherDX’s accused AMP<sup>TM</sup> process does not include “a second, nested PCR... using the universal primer” of the first PCR.

250. As another example, claim 1 of the ’708 Patent recites “subjecting the reaction mixture to primer extension reaction conditions...; wherein the annealing temperature for the reaction conditions is greater than a melting temperature of the at least 2 primers.” ArcherDX’s accused AMP<sup>TM</sup> process does not include reaction conditions “wherein annealing temperature for the reaction conditions is greater than a melting temperature of the at least 2 primers.”

251. As another example, claim 1 of the ’220 Patent recites “performing a second, nested PCR...using a second universal primer and at least 10 inner target-specific primers..., wherein at least one of the primers comprises a sequencing tag.” ArcherDX’s accused AMP<sup>TM</sup> process does not include “a second, nested PCR...wherein at least one of the [second universal primer and at least 10 inner target-specific primers] comprises a sequencing tag.”

252. Further, the Defendants have not infringed contributorily or by inducement any valid and enforceable claim of any Asserted Patent because there is no direct infringement; ArcherDX’s accused AMP<sup>TM</sup> process does not fall within the claims of any Asserted Patent. Moreover, to the extent Natera asserts that the Defendants indirectly infringe any Asserted Patent, including by inducement of infringement, the Defendants are not liable because, at a minimum, the Defendants lack the requisite intent or knowledge to induce direct infringement of any Asserted Patent by another. The Defendants also lack the knowledge required for a finding of contributory infringement under 35 U.S.C. § 271(c).

#### **FOURTH DEFENSE (Safe Harbor)**

253. Natera’s patent infringement claims are barred in whole or in part because the alleged infringing activities fall within the safe harbor provision of 35 U.S.C. § 271(e)(1).

254. STRATAFIDE™ and PCM are in development for approval or clearance by the FDA.

255. Neither STRATAFIDE™ nor PCM is presently cleared or approved by the FDA—indeed applications for clearance or approval are not yet on file with the FDA. Both STRATAFIDE™ and PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products) require premarket approval or 510(k) approval or clearance to be sold commercially. Moreover, it is not act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention solely for uses reasonably related to the development and submission of information to the FDA for premarket approval or 510(k) approval or clearance of STRATAFIDE™ or PCM (or any other IVD oncology product in development and that utilizes the same technology as any of the Accused Products).

### **FIFTH DEFENSE (Invalidity)**

256. Each of the asserted claims of the Asserted Patents are invalid for failure to satisfy one or more conditions for patentability set forth under 35 U.S.C. including but not limited to §§ 101, 102, 103, and 112 et seq., and the rules, regulations, and laws pertaining to those provisions, including the applicable provisions of Title 37 of the Code of Federal Regulations.

257. The Asserted cfDNA Patents are invalid under 35 U.S.C. §§ 102 and/or § 103 in view of Mir, alone or in combination with additional prior art, including Wei-peng Wang et al., Multiplex Single Nucleotide Polymorphism Genotyping By Adapter Ligation-Mediated Allele-Specific Amplification, *Analytical Biochemistry* 355, 240–248 (2006) (“Wang”), Diego Spertini, Screening of Transgenic Plants by Amplification of Unknown Genomic DNA Flanking T-DNA, 27 *BioTechniques* 308 (1999) (“Spertini”) or U.S. Patent App. No. 2007/0031857

(“Makarov”), which disclose all elements of the Asserted cfDNA Patents claims. Natera disclosed Mir as one of *thousands* of references during prosecution of the Asserted cfDNA Patents. Natera did not disclose either Wang, Spertini, or Makarov to the USPTO during prosecution of the Asserted cfDNA Patents. Moreover, the Asserted cfDNA Patents are at least obvious under 35 U.S.C. § 103 given Natera’s own admissions made in court filings in this District and elsewhere, which are delineated below in the Defendants’ Counterclaims.

258. The Asserted cfDNA Patents are also not entitled to a priority date earlier than their filing date of April 30, 2019, because Natera’s provisional applications and earlier-filed applications do not comply with the requirements of 35 U.S.C § 112, as required by 35 U.S.C §§ 119 and 120.

259. The provisional applications and earlier-filed applications do not contain a written description of the claims of the Asserted cfDNA Patents or contain sufficient information to enable a person of ordinary skill in the art to which they pertain to practice the full scope of the claims of the Asserted cfDNA Patents.

260. Indeed, none of the provisional applications or earlier-filed applications disclosed or sought claims corresponding to the claims of the Asserted cfDNA Patents, which recite processes that Natera did not invent.

261. Because the Asserted cfDNA Patents are not entitled to a priority date earlier than their filing date of April 30, 2019, they are invalid under 35 U.S.C. §§ 102 and/or § 103 in further view of, for example, the following prior art, alone or in combination with additional prior art: U.S. Patent App. No. 2018/0127744 (“Hu”) or International App. No. WO 2017/205540 (“Murtaza”), which disclose all elements of the Asserted cfDNA Patents claims. Natera did not disclose either Hu or Murtaza to the USPTO during prosecution of the Asserted cfDNA Patents.

Moreover, the Asserted cfDNA Patents are at least obvious under 35 U.S.C. § 103 given Natera's own admissions made in court filings in this District and elsewhere, which are delineated below in the Defendants' Counterclaims.

262. The Asserted '708 Patent is invalid under 35 U.S.C. §§ 102 and/or § 103 in view of Iafrate" or Rabinowitz, alone or in combination with additional prior art, which disclose all elements of the '708 Patent claims. Natera disclosed a related Iafrate application (U.S. Patent App. Pub. No. 2013/0303461) and Rabinowitz as two of *thousands* of references during prosecution of the '708 Patent. Moreover, the '708 Patent is at least obvious under 35 U.S.C. § 103 given Natera's own admissions made in court filings in this District and elsewhere, which are delineated below in the Defendants' Counterclaims.

263. The Asserted '708 Patent is also not entitled to a priority date earlier than its filing date of April 30, 2019, because Natera's provisional applications and earlier-filed applications do not comply with the requirements of 35 U.S.C § 112, as required by 35 U.S.C §§ 119 and 120.

264. The provisional applications and earlier-filed applications do not contain a written description of the claims of the '708 Patent or contain sufficient information to enable a person of ordinary skill in the art to which they pertain to practice the full scope of the claims of the '708 Patent.

265. Indeed, none of the provisional applications or earlier-filed applications disclosed or sought claims corresponding to the claims of the '708 Patent, which recite processes that Natera did not invent.

#### **SIXTH DEFENSE (Prosecution History Estoppel/Disclaimer)**

266. Natera is estopped from construing the claims of the Asserted Patents to cover or include, either literally or by application of the doctrine of equivalents, products manufactured,



used, imported, sold, or offered for sale by the Defendants or methods used by the Defendants because of amendments, admissions, representations, or statements made before the USPTO during prosecution of the applications leading to the issuance of the Asserted Patents or applications related thereto, because of disclosures or language in the specifications of the Asserted Patents, and/or because of limitations in the claims of the Asserted Patents.

**SEVENTH DEFENSE  
(Limitations on Recovery)**

267. Natera's claims for damages and other remedies are limited by 35 U.S.C. §§ 286 and/or 288. Natera is barred by 35 U.S.C. § 288 from recovering costs associated with this action.

**EIGHTH DEFENSE  
(Barring of Claims for Injunctive Relief)**

268. Natera is not entitled to injunctive relief against the Defendants because any alleged injury are not immediate or irreparable, Natera has an adequate remedy at law for its alleged injury, the balance of hardships does not favor an injunction, and the public interest would be disserved by an injunction. For example, enjoining the Defendants would have significant negative impacts on public health and welfare, and would disrupt important medical research. Indeed, the Defendants' products have the potential to significantly advance cancer care.

**NINTH DEFENSE  
(License and/or Exhaustion)**

269. To the extent that any of the allegedly infringing activities is directly or indirectly related to or based on products made, sold, or provided by, or services conducted by an entity that has an express or implied license to the Asserted Patents, or to the extent that any of the allegedly infringing conduct is directly or indirectly subject to rights granted to the Defendants or another entity, Natera's claims are barred, in whole or in part, in view of such licensed rights, implied or otherwise, covenant not to sue, and/or under the doctrine of patent exhaustion.

**TENTH DEFENSE  
(No Standing)**

270. To the extent Natera does not have title to the Asserted Patents, Natera has no standing to maintain its claims.

**ELEVENTH DEFENSE  
(Actions of Others)**

271. On information and belief, Natera's claims are barred, in whole or in part, because the Defendants are not liable for the acts of others over whom they have no control.

**TWELFTH DEFENSE  
(No Exceptional Case)**

272. Natera cannot prove that this is an exceptional case that justifies an award of attorney fees against the Defendants pursuant to 35 U.S.C. § 285.

**THIRTEENTH DEFENSE  
(Unclean Hands)**

273. Natera's patent infringement claims are barred in whole or in part under the doctrine of unclean hands.

**The '814 Patent and the '172 Patent**

274. As particularized below, the '814 Patent and the '172 Patent are the results of protracted and convoluted prosecution at the USPTO spanning more than a decade, and involving 16 provisional patent applications and 10 continuation or continuation-in-part applications, almost half of which were abandoned.

275. The '814 Patent and the '172 Patent are continuations of U.S. Patent App. No. 16/140,298 filed September 24, 2018.

276. U.S. Patent App. No. 16/140,298 is a continuation of U.S. Patent App. No. 14/918,544, filed October 20, 2015.

277. U.S. Patent App. No. 14/918,544 is a continuation-in-part of U.S. Patent App. No. 14/877,925, filed October 7, 2015, which is now abandoned; a continuation-in-part of U.S. Patent App. No. 14/692,703, filed April 21, 2015; and a continuation-in-part of U.S. Patent App. No. 14/538,982. U.S. Patent App. No. 14/918,544 claims priority to U.S. Provisional App. No. 62/147,377, filed April 14, 2015; U.S. Provisional App. No. 62/146,188, filed April 10, 2015; and U.S. Provisional App. No. 62/066,514, filed October 21, 2014.

278. U.S. Patent App. No. 14/877,925 is a continuation-in-part of U.S. Patent App. No. 14/255,356, filed March 25, 2014, which is now abandoned after the applicant failed to respond to any office action in prosecution; a continuation-in-part of U.S. Patent App. No. 13/780,022, filed February 28, 2013, which is now abandoned; and a continuation of U.S. Patent App. No. 13/683,604, filed November 21, 2012, which is now abandoned.

279. U.S. Patent App. No. 14/692,703 claims priority to U.S. Provisional App. No. 62/148,173, filed April 15, 2015; U.S. Provisional App. No. 62/147,377, filed April 14, 2015; U.S. Provisional App. No. 62/146,188, filed April 10, 2015; U.S. Provisional App. No. 62/066,514, filed October 21, 2014; U.S. Provisional App. No. 61/994,791, filed May 16, 2014; U.S. Provisional App. No. 61/987,407, filed May 1, 2014; and U.S. Provisional App. No. 61/982,245, filed April 21, 2014.

280. U.S. Patent App. No. 14/538,982 claims priority to U.S. Provisional App. No. 62/066,514, filed October 21, 2014; U.S. Provisional App. No. 61/994,791, filed May 16, 2014; U.S. Provisional App. No. 61/987,407, filed May 1, 2014; and U.S. Provisional App. No. 61/982,245, filed April 21, 2014.

281. U.S. Patent App. No. 14/255,356 is a continuation of PCT Application PCT/US2012/58578, filed October 3, 2012.

282. U.S. Patent App. No. 13/780,022 is a continuation-in-part of U.S. Patent App. No. 13/683,604, filed November 21, 2012, which is now abandoned; a continuation-in-part of PCT Application No. PCT/US2012/58578, filed October 3, 2012; a continuation-in-part of U.S. App. No. 13/335,043, filed December 22, 2011; a continuation-in-part of U.S. Patent App. No. 13/300,235, filed November 18, 2011; and a continuation-in-part of U.S. App. No. 13/110,685, filed May 18, 2011; and claims priority to U.S. Provisional App. No. 61/634,431, filed February 29, 2012.

283. U.S. Patent App. No. 13/683,604 is a continuation-in-part of U.S. Patent App. No. 13/300,235, filed November 18, 2011; a continuation-in-part of U.S. App. No. 13/110,685, filed May 18, 2011; and claims priority to U.S. Provisional App. No. 61/675,020, filed July 24, 2012.

284. PCT Application PCT/US2012/58578 is a continuation-in-part of U.S. Patent App. No. 13/300,235, filed November 18, 2011; and claims priority to U.S. Provisional App. No. 61/683,331, filed August 15, 2012; and U.S. Provisional App. No. 61/542,508, filed October 3, 2011.

285. U.S. Patent App. No. 13/335,043 is a continuation-in-part of U.S. Patent App. No. 13/300,235, filed November 18, 2011; a continuation-in-part of U.S. Patent App. No. 13/110,685, filed May 18, 2011; and claims priority to U.S. Provisional App. No. 61/426,208, filed December 22, 2010.

286. U.S. Patent App. No. 13/300,235 is a continuation-in-part of U.S. Patent App. No. 13/110,685, filed May 18, 2011; and claims priority to U.S. Provisional App. No. 61/542,508, filed October 3, 2011; and U.S. Provisional App. No. 61/571,248, filed June 23, 2011.

287. U.S. Patent App. No. 13/110,685 claims priority to U.S. Provisional App. No. 61/516,996, filed April 12, 2011; U.S. Provisional App. No. 61/448,547, filed March 2, 2011; U.S. Provisional App. No. 61/462,972, filed February 9, 2011; U.S. Provisional App. No. 61/398,159, filed June 21, 2010; and U.S. Provisional App. No. 61/395,850, filed May 18, 2011.

288. In connection with the above applications, Natera filed hundreds of proposed claims with the USPTO.

289. Prior to the filing of the '814 Patent application and the '172 Patent application on April 30, 2019, Natera had never disclosed nor sought claims corresponding to the claims of the '814 Patent or '172 Patent.

290. On information and belief, Natera drafted the claims of the '814 Patent and the '172 Patent in an egregious attempt to cover ArcherDX's proprietary AMP<sup>TM</sup> process—a method of amplifying DNA that Natera did not invent.

291. Indeed, Natera filed the '814 and the '172 Patent applications only after one of its senior executives left Natera, began working for ArcherDX, gained access to confidential information relating to ArcherDX's Accused Products and then returned to Natera.

### **The '482 Patent**

292. As particularized below, the '482 Patent is the result of protracted and convoluted prosecution at the USPTO spanning close to a decade, and involving 8 provisional patent applications and 4 continuation or continuation-in-part applications.

293. The '482 Patent is a continuation of U.S. Patent App. No. 16/012,667 filed June 19, 2018.

294. U.S. Patent App. No. 16/012,667 is a continuation of U.S. App. No. 13/335,043, filed December 22, 2011; a continuation-in-part of U.S. Patent App. No. 13/300,235, filed November 18, 2011; and a continuation-in-part of U.S. App. No. 13/110,685, filed May 18, 2011.

295. U.S. Patent App. No. 13/335,043 is a continuation-in-part of U.S. Patent App. No. 13/300,235, filed November 18, 2011; a continuation-in-part of U.S. Patent App. No. 13/110,685, filed May 18, 2011; and claims priority to U.S. Provisional App. No. 61/426,208, filed December 22, 2010.

296. U.S. Patent App. No. 13/300,235 is a continuation-in-part of U.S. Patent App. No. 13/110,685, filed May 18, 2011; and claims priority to U.S. Provisional App. No. 61/542,508, filed October 3, 2011; and U.S. Provisional App. No. 61/571,248, filed June 23, 2011.

297. U.S. Patent App. No. 13/110,685 claims priority to U.S. Provisional App. No. 61/516,996, filed April 12, 2011; U.S. Provisional App. No. 61/448,547, filed March 2, 2011; U.S. Provisional App. No. 61/462,972, filed February 9, 2011; U.S. Provisional App. No. 61/398,159, filed June 21, 2010; and U.S. Provisional App. No. 61/395,850, filed May 18, 2011.

298. In connection with the above applications, Natera filed hundreds of proposed claims with the USPTO.

299. Prior to the filing of the '482 Patent application on April 30, 2019, Natera had never disclosed nor sought claims corresponding to the claims of the '482 Patent.

300. On information and belief, Natera drafted the claims of the '482 Patent in an egregious attempt to cover ArcherDX's proprietary AMP<sup>TM</sup> process—a method of amplifying DNA that Natera did not invent.

301. Indeed, Natera filed the '482 Patent application only after one of its senior executives left Natera, began working for ArcherDX, gained access to confidential information relating to ArcherDX's Accused Products and then returned to Natera.

### **The '708 Patent**

302. As particularized below, the '708 Patent is the result of protracted and convoluted prosecution at the USPTO for close to 6 years, and involving multiple provisional and continuation patent applications.

303. The '708 Patent is a continuation of U.S. Patent App. No. 15,336,630 filed October 27, 2016; a continuation of application No. 14/538,982, filed on November 24, 2014.

304. U.S. Patent App. No. 14/538,982 claims priority to U.S. Provisional App. No. 62/066,514, filed October 21, 2014; U.S. Provisional App. No. 61/994,791, filed May 16, 2014; U.S. Provisional App. No. 61/987,407, filed May 1, 2014; and U.S. Provisional App. No. 61/982,245, filed April 21, 2014.

305. Prior to the filing of the '708 Patent application on April 30, 2019, Natera had never disclosed nor sought claims corresponding to the claims of the '708 Patent.

306. On information and belief, Natera drafted the claims of the '708 Patent in an egregious attempt to cover ArcherDX's proprietary AMP<sup>TM</sup> process—a method of amplifying nucleic acids that Natera did not invent.

307. Indeed, Natera filed the '708 Patent application only after one of its senior executives left Natera, began working for ArcherDX, gained access to confidential information relating to ArcherDX's Accused Products and then returned to Natera.

308. Moreover, on information and belief, Natera knew or should have known that the Asserted Patents are invalid under at least 35 U.S.C. §§ 101 and 103 given Natera's own

admissions made in court filings in this District and elsewhere, representative examples of which are set forth below in ArcherDX's Counterclaims.

309. On information and belief, Natera has improperly sought to delay competition in the IVD market by pursuing patent claims it did not invent, and subsequently prematurely asserting invalid patents that do not cover ArcherDX's products in development.

310. Based on the foregoing business misconduct, the relief Natera seeks in this action is barred by reason of its unclean hands.

### **The '220 Patent**

311. Natera's patent infringement claims are barred in whole or in part under the doctrine of unclean hands.

312. As particularized below, the '220 Patent is the result of protracted and convoluted prosecution at the USPTO spanning more than a decade, and involving 16 provisional patent applications and 11 continuation or continuation-in-part applications, almost half of which were abandoned.

313. The '220 Patent is a continuation of U.S. Patent App. No 16/399,268 filed April 30, 2019.

314. U.S. Patent App. No. 16/399,268 is a continuation of U.S. Patent App. No. 16/140,298 filed September 24, 2018.

315. U.S. Patent App. No. 16/140,298 is a continuation of U.S. Patent App. No. 14/918,544, filed October 20, 2015.

316. U.S. Patent App. No. 14/918,544 is a continuation-in-part of U.S. Patent App. No. 14/877,925, filed October 7, 2015, which is now abandoned; a continuation-in-part of U.S. Patent App. No. 14/692,703, filed April 21, 2015; and a continuation-in-part of U.S. Patent App. No. 14/538,982. U.S. Patent App. No. 14/918,544 claims priority to U.S. Provisional App.



No. 62/147,377, filed April 14, 2015; U.S. Provisional App. No. 62/146,188, filed April 10, 2015; and U.S. Provisional App. No. 62/066,514, filed October 21, 2014.

317. U.S. Patent App. No. 14/877,925 is a continuation-in-part of U.S. Patent App. No. 14/255,356, filed March 25, 2014, which is now abandoned after the applicant failed to respond to any office action in prosecution; a continuation-in-part of U.S. Patent App. No. 13/780,022, filed February 28, 2013, which is now abandoned; and a continuation of U.S. Patent App. No. 13/683,604, filed November 21, 2012, which is now abandoned.

318. U.S. Patent App. No. 14/692,703 claims priority to U.S. Provisional App. No. 62/148,173, filed April 15, 2015; U.S. Provisional App. No. 62/147,377, filed April 14, 2015; U.S. Provisional App. No. 62/146,188, filed April 10, 2015; U.S. Provisional App. No. 62/066,514, filed October 21, 2014; U.S. Provisional App. No. 61/994,791, filed May 16, 2014; U.S. Provisional App. No. 61/987,407, filed May 1, 2014; and U.S. Provisional App. No. 61/982,245, filed April 21, 2014.

319. U.S. Patent App. No. 14/255,356 is a continuation of PCT Application PCT/US2012/58578, filed October 3, 2012.

320. U.S. Patent App. No. 13/780,022 is a continuation-in-part of U.S. Patent App. No. 13/683,604, filed November 21, 2012, which is now abandoned; a continuation-in-part of PCT Application No. PCT/US2012/58578, filed October 3, 2012; a continuation-in-part of U.S. App. No. 13/335,043, filed December 22, 2011; a continuation-in-part of U.S. Patent App. No. 13/300,235, filed November 18, 2011; and a continuation-in-part of U.S. App. No. 13/110,685, filed May 18, 2011; and claims priority to U.S. Provisional App. No. 61/634,431, filed February 29, 2012.

321. U.S. Patent App. No. 13/683,604 is a continuation-in-part of U.S. Patent App. No. 13/300,235, filed November 18, 2011; a continuation-in-part of U.S. App. No. 13/110,685, filed May 18, 2011; and claims priority to U.S. Provisional App. No. 61/675,020, filed July 24, 2012.

322. PCT Application PCT/US2012/58578 is a continuation-in-part of U.S. Patent App. No. 13/300,235, filed November 18, 2011; and claims priority to U.S. Provisional App. No. 61/683,331, filed August 15, 2012; and U.S. Provisional App. No. 61/542,508, filed October 3, 2011.

323. U.S. Patent App. No. 13/335,043 is a continuation-in-part of U.S. Patent App. No. 13/300,235, filed November 18, 2011; a continuation-in-part of U.S. Patent App. No. 13/110,685, filed May 18, 2011; and claims priority to U.S. Provisional App. No. 61/426,208, filed December 22, 2010.

324. U.S. Patent App. No. 13/300,235 is a continuation-in-part of U.S. Patent App. No. 13/110,685, filed May 18, 2011; and claims priority to U.S. Provisional App. No. 61/542,508, filed October 3, 2011; and U.S. Provisional App. No. 61/571,248, filed June 23, 2011.

325. U.S. Patent App. No. 13/110,685 claims priority to U.S. Provisional App. No. 61/516,996, filed April 12, 2011; U.S. Provisional App. No. 61/448,547, filed March 2, 2011; U.S. Provisional App. No. 61/462,972, filed February 9, 2011; U.S. Provisional App. No. 61/398,159, filed June 21, 2010; and U.S. Provisional App. No. 61/395,850, filed May 18, 2011.

326. In connection with the above applications, Natera filed hundreds of proposed claims with the USPTO.

327. Prior to the filing of the '220 Patent application on January 15, 2020, Natera had never disclosed methods nor sought claims corresponding to the claims of the '220 Patent.

328. On information and belief, Natera drafted the claims of the '220 Patent in an egregious attempt to cover ArcherDX's proprietary AMP<sup>TM</sup> process—a method of amplifying DNA that Natera did not invent.

329. Indeed, Natera filed the '220 Patent application only after one of its senior executives left Natera, began working for ArcherDX, gained access to confidential information relating to ArcherDX's Accused Products and then returned to Natera.

330. Moreover, on information and belief, Natera knew or should have known that the Asserted Patent is invalid under at least 35 U.S.C. §§ 101 and 103 given Natera's own admissions made in court filings in this District and elsewhere, representative examples of which are set forth below in ArcherDX's Counterclaims.

331. On information and belief, Natera has improperly sought to delay competition in the IVD market by pursuing patent claims it did not invent, and subsequently prematurely asserting invalid patents that do not cover ArcherDX's products in development.

332. Based on the foregoing business misconduct, the relief Natera seeks in this action is barred by reason of its unclean hands.

**FOURTEENTH DEFENSE  
(Prosecution Laches)**

333. Natera's patent infringement claims are barred in whole or in part under the doctrine of prosecution laches.

334. As described above, on information and belief, Natera engaged in an unreasonable and undue delay in the prosecution of the Asserted Patents, which have prejudiced the Defendants. Thus, as a matter of equity, the Asserted Patents cannot be enforced against the Defendants.

**FIFTEENTH DEFENSE  
(Inequitable Conduct)**

335. The '220, '172, '482, and '814 patents are unenforceable due to Natera's inequitable conduct during prosecution of these patents.

336. On information and belief, Dr. Matthew Rabinowitz is the Executive Chairman, founder, and former-CEO of Natera, as well as a named inventor on the '220 Patent. Dr. Rabinowitz had a general duty of candor and good faith in his dealings with the USPTO. Pursuant to 37 C.F.R. § 1.56, an inventor has an affirmative obligation to disclose to the USPTO all information known to be material to the examination of a pending patent application. On January 15, 2020, in connection with the application that led to the '220 Patent, Dr. Rabinowitz filed an Inventor's Oath or Declaration with the USPTO pursuant to 37 C.F.R. § 1.63, acknowledging that he was "aware of the duty to disclose to the Office all information known to the person to be material to patentability."

337. According to Natera's Form 10-Q for the quarterly period ended June 30, 2020 dated August 6, 2020, "Dr. Rabinowitz spends significant time with [Natera] and is active in [Natera's] management." Ex. 14 at 68; *see also id.* at 67-68 ("If we lose the services of our founder and Executive Chairman or other members of our senior management team, we may not be able to execute our business strategy.").

338. On information and belief, as a named inventor on the patents in dispute and the Executive Chairman of Natera and someone active in Natera's management, Dr. Rabinowitz was aware of the ongoing action between Natera and ArcherDX captioned *Natera, Inc., v. ArcherDX, Inc.*, No. 1:20-cv-125 (D. Del.), including (1) ArcherDX's Answer filed on March 25, 2020 (D.I. 14) ("Answer"), (2) ArcherDX's Answer to the First Amended Complaint filed on May 13, 2020 (D.I. 21) ("Answer to FAC"), (3) ArcherDX's Opening Brief in Support of its Motion for

Judgment on the Pleadings filed on June 4, 2020 (D.I. 24) (“12(c) Motion”), and (4) ArcherDX’s Reply Brief in Support of its Motion for Judgment on the Pleadings filed on July 30, 2020 (D.I. 24) (“12(c) Reply”). On information and belief, by reason of his position as an inventor and the Executive Chairman of Natera and as someone active in Natera’s management, Dr. Rabinowitz knew of the arguments set forth in these filings while the ’220 Patent was still in prosecution before the USPTO.

339. ArcherDX, Inc.’s Answer, Answer to FAC, 12(c) Motion, and 12(c) Reply set forth invalidity arguments under 35 U.S.C. §§ 101, 103, and 112 for patents closely related to the Asserted Patent, including U.S. Patent No. 10,538,814 (the “’814 Patent”) of which the Asserted Patent is a continuation, and on which Dr. Rabinowitz is also named as an inventor.

340. ArcherDX Inc.’s Answer, Answer to FAC, 12(c) Motion, and 12(c) Reply set forth arguments that the ’814 Patent, which is directed to the same unpatentable matter as the ’220 Patent, is not patentable under § 101. For example, they set forth that claims directed to a “method of amplifying and sequencing” cell-free DNA comprising (1) ligating adaptors to cell free DNA, (2) performing a first round of PCR, (3) performing a second round of nested PCR, and (4) performing high-throughput sequencing are directed to unpatentable subject matter. *See* 12(c) Motion at 13-15 (“The asserted claims begin with naturally occurring cfDNA and, after amplification and detection, end with the same genetic information; the purpose of the claim is to detect.”); 12(c) Reply at 8; Answer to FAC at Counterclaims ¶¶ 17-22. The Answer, Answer to FAC, 12(c) Motion, and 12(c) Reply set forth that such claims are directed to the natural phenomenon of detecting cell-free DNA and utilize well-known techniques of amplification and sequencing. *See* 12(c) Motion at 16-19 (“[T]he claims recite the use of generic, well-known elements such as ‘primers,’ ‘adaptors,’ and ‘sequencing tags’ for use in conventional and routine

‘PCR’ and ‘high-throughput sequencing.’”); 12(c) Reply at 9-10; Answer to FAC at Counterclaims ¶¶ 17-22. Further, they highlighted statements made by Natera in other litigation arguing the same. *See* 12(c) Motion at 16-18 (“Natera’s admissions readily show that each method step was routine.”); 12(c) Reply at 9-10; Answer to FAC at ¶ 37.

341. ArcherDX’s Answer and Answer to FAC set forth arguments that the ’814 Patent, which claims highly similar methods to the ’220 Patent, is invalid under § 103. For example, they set forth that the prior art of Mir alone or Mir in a specific combination with Wang, Spertini, or Makarov, discloses all elements of the ’814 Patent claims. *See* Answer to FAC at Counterclaims ¶¶ 23-25. The Answer and Answer to FAC also set forth that Mir disclosed the elements that the USPTO’s examiner mistakenly stated were not in the prior art, such as, the “amplification of . . . circulating nucleic acids,” “sequencing steps, . . . incorporat[ing] a universal or common primer, and . . . a sequencing tag,” and “‘nested PCR’ following the recited ‘first PCR of ‘cell-free DNA.’” *See id.* at ¶ 37, 44. The Answer, Answer to FAC, 12(c) Motion, and 12(c) Reply also highlighted statements made by Natera in other litigation describing claim elements as routine and conventional and, hence, part of the state of the art and within the person of ordinary skill in the art’s skill. *See* 12(c) Motion at 16-18 (“Natera’s admissions readily show that each method step was routine.”); 12(c) Reply at 9-10; Answer to FAC at ¶ 37.

342. ArcherDX Inc.’s Answer and Answer to FAC set forth arguments that the ’814 Patent is invalid under § 112. For example, they set forth that the ’814 Patent, which shares a specification with the ’220 Patent, does not disclose (a) an embodiment corresponding to the claimed methods, (b) that the named inventors were in possession of the alleged invention, or (c) sufficient information to enabled a person of ordinary skill in the art to practice the claims. *See*

Answer to FAC at Counterclaims ¶¶ 26-31. The Answer and Answer to FAC set forth that the claims were not entitled to a priority date earlier than the filing date. *See id.* at Counterclaims ¶ 25.

343. On information and belief, as the Executive Chairman of Natera and someone active in Natera's management, Dr. Rabinowitz was also aware of the ongoing action between Natera and CareDX captioned *CareDX, Inc. et al. v. Natera, Inc.*, No. 19-cv-567 (D. Del.), including (1) Natera's Reply in Support of Motion to Dismiss filed on June 24, 2019 (D.I. 19), (2) Natera's Objections to Report and Recommendations filed on February 24, 2020 (D.I. 63), (3) Natera's Opening Brief in Support of Renewed Motion to Dismiss filed on April 9, 2020 (D.I. 87), (4) Natera's Opening Brief in Support of Summary Judgment of Invalidity filed on June 11, 2020 (D.I. 101), and (5) Natera's Statement re Motion for Summary Judgment of Invalidity filed on June 11, 2020 (D.I. 102) (collectively, "CareDX Briefing"). On information and belief, by reason of his position as the Executive Chairman of Natera and as someone active in Natera's management, Dr. Rabinowitz knew of Natera's own arguments set forth in these filings while the '220 Patent was still in prosecution before the USPTO.

344. Natera's CareDX Briefing sets forth arguments for invalidity under 35 U.S.C. § 101 for patents claiming methods of detecting cell-free DNA, including statements of what was "routine" and "conventional" as of 2009 and 2010, prior to the earliest possible priority date for the claims of the '220 Patent.

345. On information and belief, as the Executive Chairman of Natera and someone active in Natera's management, Dr. Rabinowitz was aware of the action between Natera and Illumina, captioned *Illumina, Inc. v. Natera, Inc.*, No. 18-cv-01662 (N.D. Cal.), including (1) Natera's Motion to Dismiss filed May 17, 2018 (D.I. 24), and (2) Natera's Reply in Support of Motion to Dismiss filed June 7, 2018 (D.I. 35) (collectively, "Illumina Briefing"). On information

and belief, by reason of his position as the Executive Chairman of Natera and as someone active in Natera's management, Dr. Rabinowitz knew of Natera's own arguments set forth in these filings while the '220 Patent was still in prosecution before the USPTO.

346. Natera's Illumina Briefing sets forth arguments for invalidity under 35 U.S.C. § 101 for a patent claiming methods of amplifying and sequencing DNA, including statements of what was "routine" and "conventional" as of 2010, prior to the earliest possible priority date for the claims of the '220 Patent.

347. Despite knowing of the arguments set forth in ArcherDX Inc.'s Answer, Answer to FAC, 12(c) Motion, and 12(c) Reply, as well as Natera's CareDX Briefing and Natera's Illumina Briefing, Dr. Rabinowitz failed to disclose any of these documents to the USPTO during prosecution of the '220 Patent.

348. Dr. Rabinowitz's failure to disclose these documents to the USPTO was but-for material to the issuance of the '220 Patent. If the USPTO had been made aware of these documents setting forth arguments for invalidity under §§ 101, 103, and 112, the '220 Patent would not have issued.

349. As set forth in the Defendants' Counterclaims filed herewith (¶¶ 17-22), the arguments presented in ArcherDX Inc.'s Answer, Answer to FAC, 12(c) Motion, and 12(c) Reply, as well as Natera's statements made in the Illumina Briefing and the CareDX Briefing establish that the claims of the '220 Patent are unpatentable under § 101 (and, as detailed below, support a finding that these claims are obvious). For example, Archer's 12(c) motion includes the following table highlighting Natera's admissions that elements of the '814 Patent, which correspond to elements of the '220 Patent, are routine or conventional:

'814 Claim Language	Natera Admissions
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1. A method for amplifying and sequencing DNA, comprising:	
ligating adaptors to cell-free DNA isolated from a biological sample, wherein the adaptors each comprises a universal priming site;	“The DNA in the sample may have <b>ligation adapters</b> ... appended, wherein <b>the ligation adapters contain a universal priming sequence</b> , followed by a universal amplification... this may be done <b>using a standard protocol designed to create sequencing libraries.</b> ” ’814 Patent, 94:11-16.
performing a first PCR to simultaneously amplify at least 10 target loci using a universal primer and at least 10 target-specific primers in a single reaction volume;	<p>“The specification lists several <b>well-known PCR techniques</b> that can be used to carry out the claimed method, such as ‘... <b>multiplex PCR.</b>’” Illumina Mot., 7.</p> <p>“<b>Primers routinely</b> are used in these amplification methods to bind to the <b>regions of a DNA strand where the DNA sequences of interest are located.</b>” Illumina Mot., 7.</p> <p>“Universal amplification of DNA using ligated adaptors <b>with primers specific to the adaptor tags</b>,... has the effect of enriching the proportion of shorter DNA strands... [E]xample protocols <b>are published and well known to those in the art.</b>” ’814 Patent, 212:14-21.</p> <p>“In some embodiments [the commercially available] QIAGEN <b>Multiplex PCR Kit</b> is used...” ’814 Patent, 235:15-16.</p>
performing a second, nested PCR to simultaneously amplify the at least 10 target loci using the universal primer and at least 10 inner target-specific primers in a single reaction volume,	<p>(Same as above)</p> <p>“[R]unning <b>multiple cycles of amplification</b> to copy DNA sequences was <b>routine and conventional.</b>” Illumina Reply, 7.</p> <p>“The specification lists several <b>well-known PCR techniques</b>... such as... multiplex PCR, or <b>nested PCR.</b>” Illumina Mot., 7.</p>
wherein at least one of the primers comprises a sequencing tag;	“It is also <b>routine and conventional</b> in the art to attach to the primers what are known as <b>sequence ‘tag[s].’</b> ” Illumina Mot., 7.
performing high-throughput sequencing to sequence the amplified DNA comprising the target loci.	“[T]he asserted claims recite nothing more than <b>conventional techniques</b> , such as... <b>high throughput sequencing.</b> ” CareDX Reply, 6-7.

If Dr. Rabinowitz had disclosed these documents to the USPTO, the USPTO would not have issued the claims.

350. As set forth in the Defendants' Counterclaims filed herewith (¶¶ 23-25), the arguments presented in ArcherDX Inc.'s Answer and Answer to FAC establish that the claims of the '220 Patent are invalid as obvious under § 103. For example, ArcherDX Inc.'s Answer and Answer to the FAC disclose that the elements of the claims of the '220 Patent that the USPTO's examiner concluded were missing from the prior art, namely "multiplex using universal or common primers and a second step of nested amplification on the same multiplex amplified targets," are indeed disclosed in the prior art, including in Mir. Archer DX's Answer ¶ 31; ArcherDX Inc.'s Answer to FAC ¶¶ 37, 44. While Natera disclosed Mir to the USPTO, it was buried in thousands of references disclosed during prosecution of the '220 Patent. By way of another example, ArcherDX Inc.'s Answer and Answer to the FAC highlighted statements made by Natera in other litigations describing elements found in the '220 Patent claims as routine and conventional. Archer DX Inc.'s Answer ¶ 31; ArcherDX's Answer to FAC ¶¶ 37. Archer's 12(c) Motion and 12(c) Reply further highlight specific admissions by Natera that the elements of the claims of the '220 Patent that the examiner concluded were missing from the prior art were routine and conventional prior to the earliest claimed priority of the '220 Patent. *See* 12(c) Motion at 16-18 ("The specification lists several well-known PCR techniques... such as... nested PCR" and "It is also routine and conventional in the art to attach to the primers what are known as sequence 'tag[s].'"); *see also* 12(c) Reply at 9. If Dr. Rabinowitz had disclosed these documents to the USPTO, the USPTO would not have issued the claims.

351. As set forth in the Defendants' Counterclaims filed herewith (¶¶ 26-31), the arguments presented in ArcherDX's Answer and Answer to FAC establish that the claims of the '220 Patent are invalid under § 112 for lack of written description and enablement. If

Dr. Rabinowitz had disclosed these documents to the USPTO, the USPTO would not have issued the claims.

352. Upon information and belief, Dr. Rabinowitz knew that he had a duty to disclose these documents to the USPTO. Indeed, some litigation documents, including some filings from the Illumina action, were disclosed to the USPTO during prosecution of the '220 Patent. For example, Natera's "Motion to Dismiss" and "Opening Brief in Support of Motion to Dismiss" filed on May 16, 2019, briefing related to its motion to dismiss under 35 U.S.C. § 101, in the Illumina action was disclosed to the USPTO during prosecution. Moreover, Natera's "First Amended Answer, Affirmative Defenses and Counterclaims" filed August 16, 2018, its Answer in the Illumina action, was also disclosed to the USPTO during prosecution. These disclosures show that, as the Executive Chairman of Natera and someone active in Natera's management, Dr. Rabinowitz understood that Answers and briefing related to § 101 motions can be material to patentability and must be disclosed to the USPTO. Despite this, Dr. Rabinowitz failed to disclose any of the documents described above (¶¶ 197-205) that are material to patentability. The single most reasonable inference able to be drawn from these facts is that Dr. Rabinowitz's failure to disclose was the result of a specific intent to deceive the USPTO.

353. Dr. Rabinowitz engaged in inequitable conduct in the prosecution of the Asserted Patent. Thus, the Asserted Patent is unenforceable.

354. The '220, '814, '172, and '482 patents are further unenforceable due to inequitable conduct in connection with Natera's June 25, 2021 submissions of documents to the patent office to alter the named inventors on these patents.

355. In these June 25 filings, Natera made major changes to the patent inventorship group, including in some cases adding Johan Baner, Milena Banjevic, Allison Ryan, and Zachary

Demko as named inventors and removing Joshua Babiarz, Tudor Constantin, Lane Eubank, Huseyin Kirkizlar, and Onur Sakarya as named inventors.

356. Natera's change of inventorship was done with deceptive intent to name on the patents a false inventorship group consisting solely of individuals who worked at Natera in a time frame consistent with the October 2011 priority date upon which Natera wishes to rely upon in this case to avoid prior art.

357. By removing as inventors several individuals that were not even affiliated with Natera until long after Natera's desired invention date and adding individuals who were, Natera seeks to avoid any inference that its alleged invention post-dates the prior art relied upon in this case by Defendants. Indeed, in connection with its attempt to correct inventorship Natera failed to submit to the Patent Office Defendants' invalidity contentions and failed to notify the Patent Office of the serious questions regarding Natera's priority claim and invention date that have been raised in the instant litigation.

358. For example, Defendants' April 2021 invalidity contentions disputed Natera's priority claim. *See, e.g.*, Ex. 9 at 4-6, 44-48. Accordingly, Defendants relied upon several highly relevant prior art references post-dating the October 2011 invention date upon which Natera now seeks to rely, including work done at Massachusetts General Hospital

359. What's more, Defendants informed Natera of the inconsistency between Natera's allegations of conception and its inventorship group as early as January 2021:

Across Natera's five asserted patents, there are 17 different named inventors, including several individuals who did not work at the company until long after the filing of the 2010 applications to which Natera's patents claim priority.

D.I. 107 at 1.

360. Defendants did so again in March 2021:

What's more, of these five listed inventors, at least four only started working at Natera long after Natera's alleged conception date of November 18, 2011. For example, based on social media profiles, Joshua Babiarez started at Natera in December 2012, Tudor Constantin in 2013, and Lane Eubank and Onur Sakarya in 2014. See Exs. C–F. It appears that Natera has systematically excluded from its inventorship contentions any individual who started working at Natera after the date that Natera now wishes to rely upon for conception. When one considers the lack of substance in Natera's non-asserted dependent claims, there is thus a major inconsistency between Natera's original representations to the Patent Office about who the inventors are and the position Natera is now taking in this case. This casts considerable doubt upon Natera's claims that the inventions of the asserted claims were truly made by November 18, 2011.

D.I. 160 at 2.

361. Three months later, when Natera sought to correct inventorship, it did not inform the Patent Office of these inconsistencies, confirming that Natera's submissions to change inventorship on the '220, '482, '172, and '841 patents were made with deceptive intent. The individuals at Natera responsible for this attempt to improperly change the inventorship group include at least Anton Bokal, Tianran Yan, Matthew Rabinowitz, Bernhard Zimmerman, George Gemelos, and Zachary Demko.

362. The deposition testimony of the several originally named inventors taken to date confirms that Natera's recent change of inventorship was done with deceptive intent.

363. Natera's senior director of scientific communications and clinical research, Zachary Demko, was head of intellectual property and a patent agent at Natera during the time frame when Natera allegedly made the inventions of the '220, '482, '172, and '841 patents. According to Dr. Demko, Natera is careful and takes steps to make sure that Natera names the right inventors on its patent applications when it seeks patent protection. *See* Ex. 10 at 105:7-109:17. Likewise, Tudor Constantin confirmed that he consulted with Natera attorneys before originally being named as an inventor on the patent. *See* Ex. 11 at 103:11-104:13, 108:2-109:8. There is thus little

reason to believe Natera identified an erroneous inventorship group when it originally filed for the '220, '482, '172, and '841 patents. Certainly, there is little reason to believe that Natera made such gross errors with respect to its inventorship identification.

364. Consistent with this, the testimony of several of the removed inventors establishes that they contributed to the alleged inventions of the '220, '482, '172, and '841 patents.

365. [REDACTED]

[REDACTED]

366. [REDACTED]

[REDACTED]

367. [REDACTED]

[REDACTED]

368. [REDACTED]

[REDACTED]

369. [REDACTED]

[REDACTED]

370.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

371.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

372. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

373. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

374. While the evidence shows that the individuals Natera now wishes to remove and has omitted as inventors participated in work directly related to the alleged inventions of the '220, '482, '172, and '841 patents, Natera's efforts to have the inventorship group involved no substantive inquiry into such efforts.

375. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



[REDACTED]

[REDACTED]

376. [REDACTED]

[REDACTED]

377. [REDACTED]

[REDACTED]

[REDACTED]

378. [REDACTED]

[REDACTED]

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379. [REDACTED]

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380. [REDACTED]

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381. [REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

382. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED] [REDACTED] [REDACTED]

[REDACTED] [REDACTED]

[REDACTED] [REDACTED]

[REDACTED] [REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

383. Such testimony underscores the dubiousness of Natera's attempt to change the inventorship groups on the '814, '482, '172, and '220 patents. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED] With respect to all of the foregoing witnesses discussed herein, Natera asserted the attorney-client privilege as to any substantive information regarding inventorship.

384. The testimony-to-date of the inventors establishes that Natera has requested that several inventors withdraw their status as inventors without any basis related to the technical contributions these individuals made to the alleged inventions of the '814, '482, '172, and '220

patents. Rather, Natera's motive in making this request was simply to remove inventors that would jeopardize its ability to improperly claim the benefit of an earlier alleged invention date. This was done with deceptive intent. This deceptive intent and bad faith is shown at least by (1) the testimony from the allegedly improperly included inventors establishing that they contributed to the claimed inventions '814, '482, '172, and '220 patents, (2) the testimony from the allegedly improperly omitted inventor establishing that she did not contribute to the claimed inventions of the '814, '482, '172, and '220 patents, (3), the testimony from the allegedly improperly included and omitted inventors establishing that they signed the documents to change inventorship at the behest of Natera's attorneys without justification and without basis, (4) the testimony from the allegedly improperly included and omitted inventors establishing that Natera did not provide these individuals with any meaningful information in connection with the submission of documents to change inventorship, and (5) Natera's assertion of the privilege to shield discovery of information regarding the submission of documents to change inventorship.

385. Natera's misrepresentation of inventors to the Patent Office was highly material. Title 35 U.S.C. § 115 provides that "An application for patent ... shall include, or be amended to include, the name of the inventor for any invention claimed in the application." Section 115 further states, "Except as otherwise provided in this section, each individual who is the inventor or a joint inventor of a claimed invention in an application for patent shall execute an oath or declaration in connection with the application." The Manual of Patent Examining Procedure ("MPEP") thus instructs examiners to reject applications with improper inventorship. See MPEP § 2137.01 (explaining that "U.S. patent law" requires "naming of the actual inventors"). The MPEP explains that "if a determination is made that the inventive entity named in a U.S. application is not correct . . . a rejection should be made on this basis." *Id.* "As a critical

requirement for obtaining a patent, inventorship is material.” *PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc.*, 225 F.3d 1315, 1321 (Fed. Cir. 2000).

386. Likewise, Natera’s withholding of Defendants’ invalidity arguments and the fact that several of the originally named inventors were not even affiliated with Natera until long after Natera’s alleged invention date was material.

387. The Examiner responsible for handling the ’814, ’482, ’172, and ’220 patents patent appears to have been under the impression that the relevant priority date for the patents in the patent family was this time frame, stating in the notice of allowance for U.S. Patent No. 10,316,362 that the “prior art does not teach a high level of multiplex amplification of more than 1000 targets simultaneously prior to 2011.” *See* Ex. 21.

388. Had the Examiner been apprised of the fact that Natera’s original inventorship group included individuals that were not even affiliated with Natera until long after this time frame and that Natera was seeking to remove such individuals as inventors from certain patents and add other inventors to other patents, the Examiner would have more thoroughly questioned and likely rejected Natera’s priority claim and would have identified substantial prior art that invalidates the ’814, ’482, ’172, and ’220 patents. As such, Natera’s misrepresentations and withholding of information was material and the ’814, ’482, ’172, and ’220 patents are unenforceable due to inequitable conduct.

### **ARCHERDX’S COUNTERCLAIMS**

Defendants/Counterclaimants Invitae Corp. (“Invitae”) and ArcherDX, LLC (“ArcherDX”) (together, “the Counterclaimants”) assert Counterclaims against Plaintiff/Counterclaim-Defendant Natera, Inc. (“Natera”) as follows:

### **NATURE OF ACTION**

1. For its Counterclaims, the Counterclaimants seek declarations that its LIQUIDPlex™, FusionPlex® and VariantPlex® products do not infringe U.S. Patent Nos. 10,538,814 (“the ’814 Patent”), 10,557,172 (“the ’172 Patent”), 10,590,482 (“the ’482 Patent”), 10,597,708 (“the ’708 Patent”), and 10,731,220 (“the ’220 Patent”) (collectively, the “Asserted Patents”) and that the Asserted Patents are invalid.

### **PARTIES**

2. ArcherDX, LLC is a limited liability company, organized and existing under the laws of the State of Delaware. ArcherDX, Inc. was, at the time of the filing of the action, a Delaware corporation with a principal place of business at 2477 55th Street, Suite 202, Boulder, Colorado 80301.

3. Invitae is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1400 16th Street, San Francisco, CA 94103. On information and belief, and as alleged by Natera in its Second Amended Complaint, Natera is a corporation organized and existing under the laws of the state of Delaware, with its principal place of business at 201 Industrial Road, San Carlos, California 94070.

### **JURISDICTION AND VENUE**

4. This Court has subject matter jurisdiction over this action under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202 as to ArcherDX’s counterclaims against Natera pursuant to the patent laws of the United States, Title 35, United States Code, and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202. An actual, substantial, and continuing justiciable controversy exists between Natera and the Counterclaimants based on Natera having filed a Second Amended Complaint against the Counterclaimants alleging infringement of the Asserted Patents by sales of LIQUIDPlex™, FusionPlex® and VariantPlex®, for research use only, with respect to which

Counterclaimants require declaration of its rights by this Court. Specifically, the controversy concerns non- infringement and invalidity of the Asserted Patents.

5. Personal jurisdiction over Natera is proper because Natera has submitted itself to the jurisdiction of this Court by, among other things, filing the Second Amended Complaint.

6. To the extent venue is proper in the underlying patent infringement action, venue is proper here as to these Counterclaims under 28 U.S.C. §§ 1391(b)–(c) and 28 U.S.C. § 1400(b).

**FIRST COUNTERCLAIM**  
**(Declaratory Judgment of Non-Infringement of the '814 Patent)**

7. The Counterclaimants reallege and incorporates its preliminary statement, and the allegations set forth in paragraphs 1-6 of these Counterclaims as if fully restated herein.

8. In its Second Amended Complaint, Natera alleges that the Counterclaimants infringed and continue to infringe the '814 Patent by its sale of LIQUIDPlex™, FusionPlex®, and VariantPlex® for research use only.

9. The Counterclaimants have not and are not now infringing, inducing the infringement of, or contributing to the infringement of any valid and enforceable claim of the '814 Patent by its sale of LIQUIDPlex™, FusionPlex®, or VariantPlex® for research use only.

10. For example, claim 1 of the '814 Patent recites “performing a first PCR...using a universal primer” and “performing a second, nested PCR...using the universal primer and at least 10 inner target-specific primers..., wherein at least one of the primers comprises a sequencing tag.” ArcherDX’s LIQUIDPlex™, FusionPlex®, and VariantPlex® products do not employ “a second, nested PCR... using the universal primer” of the first PCR, nor do the products employ “at least one of the primers comprises a sequencing tag.”

11. The Counterclaimants further lacked and continue to lack the requisite intent or knowledge to induce or contribute to the direct infringement of the '814 Patent by another by its sale of LIQUIDPlex™, FusionPlex®, and VariantPlex® for research use only.

12. A justiciable controversy exists as to whether the Counterclaimants have infringed any valid and enforceable claim of the '814 Patent by its sale of LIQUIDPlex™, FusionPlex®, and VariantPlex® for research use only.

13. The Counterclaimants are entitled to a judgment declaring that the Counterclaimants have not directly or indirectly infringed, either literally or under the doctrine of equivalents, any valid and enforceable claim of the '814 Patent by its sale of LIQUIDPlex™, FusionPlex®, or VariantPlex® for research use only.

**SECOND COUNTERCLAIM**  
**(Declaratory Judgment of Invalidity of the '814 Patent)**

14. The Counterclaimants reallege and incorporate its preliminary statement, and the allegations set forth in paragraphs 1-13 of these Counterclaims as if fully restated herein.

15. The claims of the '814 Patent are invalid in view of the prior art and/or for failure to comply with one or more conditions for patentability set forth under 35 U.S.C. including but not limited to §§ 101, 102, 103, and 112 et seq., and the rules, regulations, and laws pertaining to those provisions, including the applicable provisions of Title 37 of the Code of Federal Regulations.

16. The Counterclaimants are entitled to judgment declaring that the claims of the '814 Patent are invalid in view of the prior art and/or for failure to comply with one or more of the requirements of the United States Patent Act set out in 35 U.S.C. §§ 1, et seq., including without limitation 35 U.S.C. §§ 101, 102, 103, and 112.

### Invalidity under 35 U.S.C. § 101

17. Accepting as true Natera’s own statements made in proceedings in this District and elsewhere, the claims of the ’814 Patent are directed to unpatentable naturally occurring subject matter, phenomena, and/or relationships, and any additional elements in the claims are merely well-understood, routine, or conventional. Thus, the claims of the ’814 Patent are unpatentable under 35 U.S.C. § 101.

18. For example, in another case pending in this District, *CareDX, Inc. et al. v. Natera, Inc.*, No. 19-cv-567 (D. Del.) (“CareDX”), Natera has alleged that the claims of the two patents-in-suit there—U.S. Patent Nos. 8,703,652 and 9,845,497—are unpatentable under 35 U.S.C. § 101. *See CareDX*, No. 19-cv-567, D.I. 9-10, 19 (Natera’s Motion to Dismiss and Briefing Related Thereto), 63 (Natera’s Objections to Report and Recommendation) (attached as Exhibits 1-4); *see also id.*, D.I. 86, 87 (Natera’s Renewed Motion to Dismiss) (attached as Exhibits 7-8). The two patents asserted in CareDX claim priority to applications filed in 2009 and 2010, which is before the earliest possible priority date for the claims of the ’814 Patent.

19. Similarly, in *Illumina, Inc. v. Natera, Inc.*, No. 18-cv-01662 (N.D. Cal.) (“Illumina”), Natera has alleged that the claims of U.S. Patent No. 9,493,831 are unpatentable under Section 101. *See Illumina*, No. 18-cv-01662, D.I. 24, 35 (Motion to Dismiss and Briefing Related Thereto) (attached as Exhibits 5-6). The patent asserted in Illumina claims priority to an application filed in 2010, which is before the earliest possible priority date for the claims of the ’814 Patent.

20. In this case, representative claim 1 of the ’814 Patent recites a “a method for amplifying and sequencing DNA” comprising (1) ligating adaptors to isolated cell-free DNA, (2) performing a first round of polymerase chain reaction (PCR), (3) performing a second, “nested”



round of PCR that includes use of a sequencing tag, and (4) performing high-throughput sequencing to sequence the cell-free DNA.

21. But in *CareDX*, Natera itself acknowledged that cell-free DNA is a natural phenomenon, and alleged that amplification and sequencing methods, such as PCR and high throughput sequencing, were known and used in the art to detect and sequence cell-free DNA. *E.g.*, *CareDX*, D.I. 10 at 12-19; D.I. 19 at 6-7; D.I. 63 at 3-5. And in *Illumina*, Natera also argued that cell-free DNA is “naturally occurring,” and the use of “well-known, routine, and conventional amplification techniques”—including nested PCR, and the use of primers with attached sequencing tags—to amplify and sequence the DNA is not patentable. *See Illumina*, No. 18-cv-01662, D.I. 24 at 2, 6-8; D.I. 35 at 2-9.

22. Thus, by Natera’s own admissions, the claims of the ’814 Patent are unpatentable under 35 U.S.C. § 101, and Natera should never have filed its Second Amended Complaint against the Counterclaimants.

### **Invalidity under 35 U.S.C. §§ 102 and 103**

23. The claims of the ’814 Patent are invalid under 35 U.S.C. § 102 and/or § 103, in view of, for example, the following prior art, alone or in combination with additional prior art: Mir, with Wang, Spertini, or Makarov, which disclose all elements of the ’814 Patent claims. Natera disclosed Mir as one of *thousands* of references during prosecution of the ’814 Patent. Natera did not disclose either Wang, Spertini, or Makarov to the USPTO during prosecution of the ’814 Patent. Moreover, the ’814 Patent is at least obvious under 35 U.S.C. § 103 given Natera’s own admissions made in court filings in this District and elsewhere, representative examples of which are set forth above in paragraphs 17-22.

24. The ’814 Patent is also not entitled to a priority date earlier than its filing date of April 30, 2019, because Natera’s provisional applications and earlier-filed applications do not

comply with the requirements of 35 U.S.C § 112, as required by 35 U.S.C §§ 119 and 120. The provisional applications and earlier-filed applications do not contain a written description of the claims of the '814 Patent or contain sufficient information to enable a person of ordinary skill in the art to which they pertain to practice the full scope of the claims of the '814 Patent. Indeed, none of the provisional applications or earlier-filed applications disclosed or sought claims corresponding to the claims of the '814 Patent, which recite processes that Natera did not invent.

25. Because the '814 Patent is not entitled to a priority date earlier than its filing date of April 30, 2019, it is invalid under 35 U.S.C. § 102 and/or § 103, in further view of, for example, the following prior art, alone or in combination with additional prior art: Hu or Murtaza, which disclose all elements of the '814 Patent claims. Natera did not disclose either Hu or Murtaza to the USPTO during prosecution of the '814 Patent. Moreover, the '814 Patent is at least obvious under 35 U.S.C. § 103 given Natera's own admissions made in court filings in this District and elsewhere, representative examples of which are set forth above in paragraphs 17-22.

26. The '814 patent is further invalid for failing to name the proper inventors under 35 U.S.C. § 102(f), as set forth above in paragraphs 354-88 of Defendants' answer.

#### **Invalidity under 35 U.S.C. § 112 and Improper Inventorship**

27. The claims of the '814 Patent are invalid under 35 U.S.C. § 112.

28. The claims of the '814 Patent lack written description support in the specification.

29. As an example, the specification of the '814 Patent does not disclose an embodiment or example corresponding to claim 1 of the '814 Patent and does not otherwise disclose that the named inventors of the '814 Patent were in possession of the alleged invention recited in the claims as of the priority date of the '814 Patent.

30. Indeed, prior to the filing of the '814 Patent application on April 30, 2019, Natera had never disclosed nor sought claims corresponding to the claims of the '814 Patent.

31. The specification also does not contain sufficient information to enable a person of ordinary skill in the art to which the patent pertains to practice the full scope of the claims of the '814 Patent.

32. The '814 Patent does not satisfy the requirements of 35 U.S.C. § 112 because the applicants for the '814 Patent did not themselves invent the subject matter sought to be patented—an independent ground for invalidating the patent.

**THIRD COUNTERCLAIM**  
**(Declaratory Judgment of Unenforceability Of The '814 Patent Due to Inequitable Conduct)**

33. The Counterclaimants reallege and incorporate its preliminary statement, and the allegations set forth in paragraphs 1-31 of these Counterclaims as if fully restated herein.

34. Defendants incorporate herein by reference the facts set forth with particularly in paragraphs 354-88 of Defendants' answer above. As alleged in the incorporated paragraphs, the '814 patent is unenforceable due to inequitable conduct.

**FOURTH COUNTERCLAIM**  
**(Declaratory Judgment of Non-Infringement of the '172 Patent)**

35. The Counterclaimants reallege and incorporate its preliminary statement, and the allegations set forth in paragraphs 1-34 of these Counterclaims as if fully restated herein.

36. In its Second Amended Complaint, Natera alleges that the Counterclaimants have infringed and continue to infringe the '172 Patent by its sale of LIQUIDPlex™, FusionPlex®, and VariantPlex® for research use only.

37. The Counterclaimants have not and are not now infringing, inducing the infringement of, or contributing to the infringement of any valid and enforceable claim of the '172 Patent by its sale of LIQUIDPlex™, FusionPlex®, or VariantPlex® for research use only.

38. For example, claim 1 of the '172 Patent recites “performing a first PCR...using a universal primer” and “performing a second, nested PCR...using the universal primer.” ArcherDX’s LIQUIDPlex™, FusionPlex®, and VariantPlex® products do not include “a second, nested PCR... using the universal primer” of the first PCR.

39. The Counterclaimants further lacked and continue to lack the requisite intent or knowledge to induce or contribute to the direct infringement of the '172 Patent by another by its sale of LIQUIDPlex™, FusionPlex®, or VariantPlex® for research use only.

40. A justiciable controversy exists as to whether the Counterclaimants have infringed any valid and enforceable claim of the '172 Patent by its sale of LIQUIDPlex™, FusionPlex®, and VariantPlex® for research use only.

41. The Counterclaimants are entitled to a judgment declaring that the Counterclaimants have not directly or indirectly infringed, either literally or under the doctrine of equivalents, any valid and enforceable claim of the '172 Patent by its sale of LIQUIDPlex™, FusionPlex®, or VariantPlex® for research use only.

**FIFTH COUNTERCLAIM**  
**(Declaratory Judgment of Invalidity of the '172 Patent)**

42. The Counterclaimants reallege and incorporate its preliminary statement, and the allegations set forth in paragraphs 1-41 of these Counterclaims as if fully restated herein.

43. The claims of the '172 Patent are invalid in view of the prior art and/or for failure to comply with one or more conditions for patentability set forth under 35 U.S.C. including but not limited to §§ 101, 102, 103, and 112 et seq., and the rules, regulations, and laws pertaining to those provisions, including the applicable provisions of Title 37 of the Code of Federal Regulations.

44. The Counterclaimants are entitled to judgment declaring that the claims of the '172 Patent are invalid in view of the prior art and/or for failure to comply with one or more of the requirements of the United States Patent Act set out in 35 U.S.C. §§ 1, et seq., including without limitation 35 U.S.C. §§ 101, 102, 103, and 112.

### **Invalidity under 35 U.S.C. § 101**

45. Accepting as true Natera's own statements made in proceedings in this District and elsewhere, the claims of the '172 Patent are directed to unpatentable naturally occurring subject matter, phenomena, and/or relationships, and any additional elements in the claims are merely well-understood, routine, or conventional. Thus, the claims of the '172 Patent are unpatentable under 35 U.S.C. § 101.

46. For example, in CareDX, Natera has alleged that the claims of the two patents-in-suit there—U.S. Patent Nos. 8,703,652 and 9,845,497—are unpatentable under 35 U.S.C. § 101. *See* Exs. 1-4, 7-8. The two patents asserted in CareDX claim priority to applications filed in 2009 and 2010, which is before the earliest possible priority date for the claims of the '172 Patent.

47. Similarly, in Illumina, Natera has alleged that the claims of U.S. Patent No. 9,493,831 are unpatentable under Section 101. *See* Exs. 5-6. The patent asserted in Illumina claims priority to an application filed in 2010, which is before the earliest possible priority date for the claims of the '172 Patent.

48. In this case, representative claim 1 of the '172 Patent recites a “a method for amplifying and sequencing DNA” comprising (1) isolating and tagging cell-free DNA with a molecular barcode, (2) performing a first round of polymerase chain reaction (PCR), (3) performing a second, “nested” round of PCR, and (4) performing high-throughput sequencing to sequence the cell-free DNA.

49. But in CareDX, Natera itself acknowledged that cell-free DNA is a natural phenomenon, and alleged that amplification and sequencing methods, such as PCR and high throughput sequencing, were known and used in the art to detect and sequence cell-free DNA. *E.g.*, *CareDX*, D.I. 10 at 12-19; D.I. 19 at 6-7; D.I. 63 at 3-5. And in Illumina, Natera also argued that cell-free DNA is “naturally occurring,” and the use of “well-known, routine, and conventional amplification techniques”—including nested PCR, and the use of primers—to amplify and sequence the DNA is not patentable. *See Illumina*, No. 18-cv-01662, D.I. 24 at 2, 6-8; D.I. 35 at 2-9.

50. Thus, by Natera’s own admissions, the claims of the ’172 Patent are unpatentable under 35 U.S.C. § 101, and Natera should never have filed its Second Amended Complaint against the Counterclaimants.

### **Invalidity under 35 U.S.C. §§ 102 and 103**

51. The claims of the ’172 Patent are invalid under 35 U.S.C. § 102 and/or § 103, in view of, for example, the following prior art, alone or in combination with additional prior art: Mir, with Wang, Spertini, or Makarov, which disclose all elements of the ’172 Patent claims. Natera disclosed Mir as one of *thousands* of references during prosecution of the ’172 Patent. Natera did not disclose either Wang, Spertini, or Makarov to the USPTO during prosecution of the ’172 Patent. Moreover, the ’172 Patent is at least obvious under 35 U.S.C. § 103 given Natera’s own admissions made in court filings in this District and elsewhere, representative examples of which are set forth above in paragraphs 45-50.

52. The ’172 Patent is also not entitled to a priority date earlier than its filing date of April 30, 2019, because Natera’s provisional applications and earlier-filed applications do not comply with the requirements of 35 U.S.C § 112, as required by 35 U.S.C §§ 119 and 120. The provisional applications and earlier-filed applications do not contain a written description of the

claims of the '172 Patent or contain sufficient information to enable a person of ordinary skill in the art to which they pertain to practice the full scope of the claims of the '172 Patent. Indeed, none of the provisional applications or earlier-filed applications disclosed or sought claims corresponding to the claims of the '172 Patent, which recite processes that Natera did not invent.

53. Because the '172 Patent is not entitled to a priority date earlier than its filing date of April 30, 2019, it is invalid under 35 U.S.C. § 102 and/or § 103, in further view of, for example, the following prior art, alone or in combination with additional prior art: Hu or Murtaza, which disclose all elements of the '172 Patent claims. Natera did not disclose either Hu or Murtaza to the USPTO during prosecution of the '172 Patent. Moreover, the '172 Patent is at least obvious under 35 U.S.C. § 103 given Natera's own admissions made in court filings in this District and elsewhere, representative examples of which are set forth above in paragraphs 45-50.

54. The '172 patent is further invalid for failing to name the proper inventors under 35 U.S.C. § 102(f), as set forth above in paragraphs 354-88 of Defendants' answer.

#### **Invalidity under 35 U.S.C. § 112 and Improper Inventorship**

55. The claims of the '172 Patent are invalid under 35 U.S.C. § 112.

56. The claims of the '172 Patent lack written description support in the specification.

57. As an example, the specification of the '172 Patent does not disclose an embodiment or example corresponding to claim 1 of the '172 Patent and does not otherwise disclose that the named inventors of the '172 Patent were in possession of the alleged invention recited in the claims as of the priority date of the '172 Patent.

58. Indeed, prior to the filing of the '172 Patent application on April 30, 2019, Natera had never disclosed nor sought claims corresponding to the claims of the '172 Patent.

59. The specification also does not contain sufficient information to enable a person of ordinary skill in the art to which the patent pertains to practice the full scope of the claims of the '172 Patent.

60. The '172 Patent does not satisfy the requirements of 35 U.S.C. § 112 because the applicants for the '172 Patent did not themselves invent the subject matter sought to be patented—an independent ground for invalidating the patent.

**SIXTH COUNTERCLAIM**  
**(Declaratory Judgment of Unenforceability Of The '172 Patent Due to Inequitable Conduct)**

61. The Counterclaimants reallege and incorporate its preliminary statement, and the allegations set forth in paragraphs 1-60 of these Counterclaims as if fully restated herein.

62. Defendants incorporate herein by reference the facts set forth with particularly in paragraphs 354-88 of their answer above. As alleged in the incorporated paragraphs, the '172 patent is unenforceable due to inequitable conduct.

**SEVENTH COUNTERCLAIM**  
**(Declaratory Judgment of Non-Infringement of the '482 Patent)**

63. The Counterclaimants reallege and incorporate its preliminary statement, and the allegations set forth in paragraphs 1-62 of these Counterclaims as if fully restated herein.

64. In its Second Amended Complaint, Natera alleges that the Counterclaimants have infringed and continue to infringe the '482 Patent by its sale of LIQUIDPlex™, FusionPlex®, and VariantPlex® for research use only.

65. The Counterclaimants have not and are not now infringing, inducing the infringement of, or contributing to the infringement of any valid and enforceable claim of the '482 Patent by its sale of LIQUIDPlex™, FusionPlex®, or VariantPlex® for research use only.



66. For example, claim 1 of the '482 Patent recites “performing a first PCR...using a universal primer” and “performing a second, nested PCR...using the universal primer.” ArcherDX’s LIQUIDPlex™, FusionPlex®, and VariantPlex® products do not employ “a second, nested PCR...using the universal primer” of the first PCR.

67. The Counterclaimants further lacked and continue to lack the requisite intent or knowledge to induce or contribute to the direct infringement of the '482 Patent by another by its sale of LIQUIDPlex™, FusionPlex®, or VariantPlex® for research use only.

68. A justiciable controversy exists as to whether the Counterclaimants have infringed any valid and enforceable claim of the '482 Patent by its sale of LIQUIDPlex™, FusionPlex®, or VariantPlex® for research use only.

69. The Counterclaimants are entitled to a judgment declaring that the Counterclaimants have not directly or indirectly infringed, either literally or under the doctrine of equivalents, any valid and enforceable claim of the '482 Patent by its sale of LIQUIDPlex™, FusionPlex®, or VariantPlex® for research use only.

**EIGHTH COUNTERCLAIM**  
**(Declaratory Judgment of Invalidity of the '482 Patent)**

70. The Counterclaimants reallege and incorporate its preliminary statement, and the allegations set forth in paragraphs 1-69 of these Counterclaims as if fully restated herein.

71. The claims of the '482 Patent are invalid in view of the prior art and/or for failure to comply with one or more conditions for patentability set forth under 35 U.S.C. including but not limited to §§ 101, 102, 103, and 112 et seq., and the rules, regulations, and laws pertaining to those provisions, including the applicable provisions of Title 37 of the Code of Federal Regulations.

72. The Counterclaimants are entitled to judgment declaring that the claims of the '482 Patent are invalid in view of the prior art and/or for failure to comply with one or more of the requirements of the United States Patent Act set out in 35 U.S.C. §§ 1, et seq., including without limitation 35 U.S.C. §§ 101, 102, 103, and 112.

**Invalidity under 35 U.S.C. § 101**

73. Accepting as true Natera's own statements made in proceedings in this District and elsewhere, the claims of the '482 Patent are directed to unpatentable naturally occurring subject matter, phenomena, and/or relationships, and any additional elements in the claims are merely well-understood, routine, or conventional. Thus, the claims of the '482 Patent are unpatentable under 35 U.S.C. § 101.

74. For example, in CareDX, Natera has alleged that the claims of the two patents-in-suit there—U.S. Patent Nos. 8,703,652 and 9,845,497—are unpatentable under 35 U.S.C. § 101. *See* Exs. 1-4, 7-8. The two patents asserted in CareDX claim priority to applications filed in 2009 and 2010, which is before the earliest possible priority date for the claims of the '482 Patent.

75. Similarly, in Illumina, Natera has alleged that the claims of U.S. Patent No. 9,493,831 are unpatentable under Section 101. *See* Exs. 5-6. The patent asserted in Illumina claims priority to an application filed in 2010, which is before the earliest possible priority date for the claims of the '482 Patent.

76. In this case, representative claim 1 of the '482 Patent recites a “a method for nested PCR amplification” comprising (1) isolating cell-free DNA; (2) ligating adaptors to isolated cell-free DNA, (3) performing a first round of polymerase chain reaction (PCR), and (4) performing a second, “nested” round of PCR.

77. But in CareDX, Natera itself acknowledged that cell-free DNA is a natural phenomenon, and alleged that amplification methods, such as PCR, were known and used in the

art to detect cell-free DNA. *E.g.*, CareDX, D.I. 10 at 12-19; D.I. 19 at 6-7; D.I. 63 at 3-5. And in Illumina, Natera also argued that cell-free DNA is “naturally occurring,” and the use of “well-known, routine, and conventional amplification techniques”—including nested PCR—to amplify and sequence the DNA is not patentable. *See Illumina*, No. 18-cv-01662, D.I. 24 at 2, 6-8; D.I. 35 at 2-9.

78. Thus, by Natera’s own admissions, the claims of the ’482 Patent are unpatentable under 35 U.S.C. § 101, and Natera should never have filed its Second Amended Complaint against the Counterclaimants.

### **Invalidity under 35 U.S.C. §§ 102 and 103**

79. The claims of the ’482 Patent are invalid under 35 U.S.C. § 102 and/or § 103, in view of, for example, the following prior art, alone or in combination with additional prior art: Mir, with Wang, Spertini, or Makarov, which disclose all elements of the ’482 Patent claims. Natera disclosed Mir as one of *thousands* of references during prosecution of the ’482 Patent. Natera did not disclose either Wang, Spertini, or Makarov to the USPTO during prosecution of the ’482 Patent. Moreover, the ’482 Patent is at least obvious under 35 U.S.C. § 103 given Natera’s own admissions made in court filings in this District and elsewhere, representative examples of which are set forth above in paragraphs 73-78.

80. The ’482 Patent is also not entitled to a priority date earlier than its filing date of April 30, 2019, because Natera’s provisional applications and earlier-filed applications do not comply with the requirements of 35 U.S.C § 112, as required by 35 U.S.C §§ 119 and 120. The provisional applications and earlier-filed applications do not contain a written description of the claims of the ’482 Patent or contain sufficient information to enable a person of ordinary skill in the art to which they pertain to practice the full scope of the claims of the ’482 Patent. Indeed,

none of the provisional applications or earlier-filed applications disclosed or sought claims corresponding to the claims of the '482 Patent, which recite processes that Natera did not invent.

81. Because the '482 Patent is not entitled to a priority date earlier than its filing date of April 30, 2019, it is invalid under 35 U.S.C. § 102 and/or § 103, in further view of, for example, the following prior art, alone or in combination with additional prior art: Hu or Murtaza, which disclose all elements of the '482 Patent claims. Natera did not disclose either Hu or Murtaza to the USPTO during prosecution of the '482 Patent. Moreover, the '482 Patent is at least obvious under 35 U.S.C. § 103 given Natera's own admissions made in court filings in this District and elsewhere, representative examples of which are set forth above in paragraphs 73-78.

82. The '482 patent is further invalid for failing to name the proper inventors under 35 U.S.C. § 102(f), as set forth above in paragraphs 354-88 of Defendants' answer.

**Invalidity under 35 U.S.C. § 112 and Improper Inventorship**

83. The claims of the '482 Patent are invalid under 35 U.S.C. § 112.

84. The claims of the '482 Patent lack written description support in the specification.

85. As an example, the specification of the '482 Patent does not disclose an embodiment or example corresponding to claim 1 of the '482 Patent and does not otherwise disclose that the named inventors of the '482 Patent were in possession of the alleged invention recited in the claims as of the priority date of the '482 Patent.

86. Indeed, prior to the filing of the '482 Patent application on April 30, 2019, Natera had never disclosed nor sought claims corresponding to the claims of the '482 Patent.

87. The specification also does not contain sufficient information to enable a person of ordinary skill in the art to which the patent pertains to practice the full scope of the claims of the '482 Patent.

88. The '482 Patent does not satisfy the requirements of 35 U.S.C. § 112 because the applicants for the '482 Patent did not themselves invent the subject matter sought to be patented—an independent ground for invalidating the patent.

**NINTH COUNTERCLAIM**  
**(Declaratory Judgment of Unenforceability Of The '482 Patent Due to Inequitable Conduct)**

89. The Counterclaimants reallege and incorporate its preliminary statement, and the allegations set forth in paragraphs 1-85 of these Counterclaims as if fully restated herein.

90. Defendants incorporate herein by reference the facts set forth with particularly in paragraphs 354-88 of their answer above. As alleged in the incorporated paragraphs, the '482 patent is unenforceable due to inequitable conduct.

**TENTH COUNTERCLAIM**  
**(Declaratory Judgment of Non-Infringement of the '708 Patent)**

91. The Counterclaimants reallege and incorporate its preliminary statement, and the allegations set forth in paragraphs 1-90 of these Counterclaims as if fully restated herein.

92. In its Second Amended Complaint, Natera alleges that ArcherDX has infringed and continues to infringe the '708 Patent by its sale of LIQUIDPlex™, FusionPlex®, and VariantPlex® for research use only.

93. The Counterclaimants have not and are not now infringing, inducing the infringement of, or contributing to the infringement of any valid and enforceable claim of the '708 Patent by its sale of LIQUIDPlex™, FusionPlex®, or VariantPlex® for research use only.

94. For example, claim 1 of the '708 Patent recites “subjecting the reaction mixture to primer extension reaction conditions...; wherein annealing temperature for the reaction conditions is greater than a melting temperature of the at least 2 primers.” ArcherDX’s LIQUIDPlex™, FusionPlex®, and VariantPlex® products do not employ reaction conditions “wherein the annealing

temperature for the reaction conditions is greater than a melting temperature of the at least 2 primers.”

95. The Counterclaimants further lacked and continue to lack the requisite intent or knowledge to induce or contribute to the direct infringement of the '708 Patent by another by its sale of LIQUIDPlex™, FusionPlex®, or VariantPlex® for research use only.

96. A justiciable controversy exists as to whether the Counterclaimants have infringed any valid and enforceable claim of the '708 Patent by its sale of LIQUIDPlex™, FusionPlex®, or VariantPlex® for research use only.

97. The Counterclaimants are entitled to a judgment declaring that the Counterclaimants have not directly or indirectly infringed, either literally or under the doctrine of equivalents, any valid and enforceable claim of the '708 Patent by its sale of LIQUIDPlex™, FusionPlex®, or VariantPlex® for research use only.

**ELEVENTH COUNTERCLAIM**  
**(Declaratory Judgment of Invalidity of the '708 Patent)**

98. The Counterclaimants reallege and incorporate its preliminary statement, and the allegations set forth in paragraphs 1-97 of these Counterclaims as if fully restated herein.

99. The claims of the '708 Patent are invalid in view of the prior art and/or for failure to comply with one or more conditions for patentability set forth under 35 U.S.C. including but not limited to §§ 101, 102, 103, and 112 et seq., and the rules, regulations, and laws pertaining to those provisions, including the applicable provisions of Title 37 of the Code of Federal Regulations.

100. The Counterclaimants are entitled to judgment declaring that the claims of the '708 Patent are invalid in view of the prior art and/or for failure to comply with one or more of the

requirements of the United States Patent Act set out in 35 U.S.C. §§ 1, et seq., including without limitation 35 U.S.C. §§ 101, 102, 103, and 112.

### **Invalidity under 35 U.S.C. § 101**

101. Accepting as true Natera’s own statements made in proceedings in this District and elsewhere, the claims of the ’708 Patent are directed to unpatentable naturally occurring subject matter, phenomena, and/or relationships, and any additional elements in the claims are merely well-understood, routine, or conventional. Thus, the claims of the ’708 Patent are unpatentable under 35 U.S.C. § 101.

102. For example, in *CareDX*, Natera has alleged that the claims of the two patents-in-suit there—U.S. Patent Nos. 8,703,652 and 9,845,497—are unpatentable under 35 U.S.C. § 101. *See* Exs. 1-4, 7-8. The two patents asserted in *CareDX* claim priority to applications filed in 2009 and 2010, which is before the earliest possible priority date for the claims of the ’708 Patent.

103. Similarly, in *Illumina*, Natera has alleged that the claims of U.S. Patent No. 9,493,831 are unpatentable under Section 101. *See* Exs. 5-6. The patent asserted in *Illumina* claims priority to an application filed in 2010, which is before the earliest possible priority date for the claims of the ’708 Patent.

104. In this case, representative claim 1 of the ’708 Patent recites “a method for amplifying target loci in a nucleic acid sample” comprising (1) contacting a nucleic acid with target-specific primers, and (2) subjecting the reaction mixture to amplification reaction conditions.

105. But in *CareDX*, Natera itself acknowledged that nucleic acids are a natural phenomenon, and alleged that amplification methods were known and used in the art to detect nucleic acids. E.g., *CareDX*, D.I. 10 at 12-19; D.I. 19 at 6-7; D.I. 63 at 3-5. And in *Illumina*, Natera also argued that nucleic acids are “naturally occurring,” and the use of “well-known, routine, and

conventional amplification techniques”—including the use of primers—to amplify the nucleic acid is not patentable. *See Illumina*, No. 18-cv-01662, D.I. 24 at 2, 6-8; D.I. 35 at 2-9.

106. Thus, by Natera’s own admissions, the claims of the ’708 Patent are unpatentable under 35 U.S.C. § 101, and Natera should never have filed its Second Amended Complaint against the Counterclaimants.

### **Invalidity under 35 U.S.C. §§ 102 and 103**

107. The claims of the ’708 Patent are invalid under 35 U.S.C. § 102 and/or § 103, in view of, for example, the following prior art, alone or in combination with additional prior art: Iafrate and Rabinowitz, which disclose all elements of the ’708 Patent claims. Natera disclosed a related Iafrate application (U.S. Patent App. Pub. No. 2013/0303461) and Rabinowitz as two of *thousands* of references during prosecution of the ’708 Patent. Moreover, the ’708 Patent is at least obvious under 35 U.S.C. § 103 given Natera’s own admissions made in court filings in this District and elsewhere, representative examples of which are set forth above in paragraphs 101-06.

108. The ’708 Patent is also not entitled to a priority date earlier than its filing date of April 30, 2019, because Natera’s provisional applications and earlier-filed applications do not comply with the requirements of 35 U.S.C § 112, as required by 35 U.S.C §§ 119 and 120. The provisional applications and earlier-filed applications do not contain a written description of the claims of the ’708 Patent or contain sufficient information to enable a person of ordinary skill in the art to which they pertain to practice the full scope of the claims of the ’708 Patent. Indeed, none of the provisional applications or earlier-filed applications disclosed or sought claims corresponding to the claims of the ’708 Patent, which recite processes that Natera did not invent.

### **Invalidity under 35 U.S.C. § 112 and Improper Inventorship**

109. The claims of the ’708 Patent are invalid under 35 U.S.C. § 112.



110. The claims of the '708 Patent lack written description support in the specification and are indefinite.

111. As an example, the specification of the '708 Patent does not disclose an embodiment or example corresponding to claim 1 of the '708 Patent and does not otherwise disclose that the named inventors of the '708 Patent were in possession of the alleged invention recited in the claims as of the priority date of the '708 Patent.

112. Indeed, prior to the filing of the '708 Patent application on April 30, 2019, Natera had never disclosed nor sought claims corresponding to the claims of the '708 Patent.

113. The specification also does not contain sufficient information to enable a person of ordinary skill in the art to which the patent pertains to practice the full scope of the claims of the '708 Patent.

114. Moreover, the claims of the '708 Patent are indefinite because the claim language, read in light of the specification and prosecution history, fails to inform, with reasonable certainty, those skilled in the art about the scope of the alleged invention.

115. The '708 Patent does not satisfy the requirements of 35 U.S.C. § 112 because the applicants for the '708 Patent did not themselves invent the subject matter sought to be patented—an independent ground for invalidating the patent.

**TWELFTH COUNTERCLAIM**  
**(Declaratory Judgment of Non-Infringement of the '220 Patent)**

116. The Counterclaimants reallege and incorporate its preliminary statement, and the allegations set forth in paragraphs 1-115 of these Counterclaims as if fully restated herein.

117. In its Complaint, Natera alleges that the Counterclaimants have infringed and continue to infringe the '220 Patent by its sale of LIQUIDPlex<sup>TM</sup> or VariantPlex<sup>®</sup> for research use only.

118. The Counterclaimants have not and is not now infringing, inducing the infringement of, or contributing to the infringement of any valid and enforceable claim of the '220 Patent by its sale of LIQUIDPlex™ or VariantPlex® for research use only.

119. For example, claim 1 of the '220 Patent recites “performing a second, nested PCR...using a second universal primer and at least 10 inner target-specific primers..., wherein at least one of the primers comprises a sequencing tag.” ArcherDX’s accused AMP™ process does not include “a second, nested PCR...wherein at least one of the [second universal primer and at least 10 inner target-specific primers] comprises a sequencing tag.”

120. The Counterclaimants further lacked and continue to lack the requisite intent or knowledge to induce or contribute to the direct infringement of the '220 Patent by another by its sale of LIQUIDPlex™ or VariantPlex® for research use only.

121. A justiciable controversy exists as to whether the Counterclaimants have infringed any valid and enforceable claim of the '220 Patent by its sale of LIQUIDPlex™ and VariantPlex® for research use only.

122. The Counterclaimants are entitled to a judgment declaring that the Counterclaimants have not directly or indirectly infringed, either literally or under the doctrine of equivalents, any valid and enforceable claim of the '220 Patent by its sale of LIQUIDPlex™ or VariantPlex® for research use only.

**THIRTEENTH COUNTERCLAIM**  
**(Declaratory Judgment of Invalidity of the '220 Patent)**

123. The Counterclaimants reallege and incorporate its preliminary statement, and the allegations set forth in paragraphs 1-122 of these Counterclaims as if fully restated herein.

124. The claims of the '220 Patent are invalid in view of the prior art and/or for failure to comply with one or more conditions for patentability set forth under 35 U.S.C. including but

not limited to §§ 101, 102, 103, and 112 et seq., and the rules, regulations, and laws pertaining to those provisions, including the applicable provisions of Title 37 of the Code of Federal Regulations.

125. The Counterclaimants are entitled to judgment declaring that the claims of the '220 Patent are invalid in view of the prior art and/or for failure to comply with one or more of the requirements of the United States Patent Act set out in 35 U.S.C. §§ 1, et seq., including without limitation 35 U.S.C. §§ 101, 102, 103, and 112.

### **Invalidity under 35 U.S.C. § 101**

126. Accepting as true Natera's own statements made in proceedings in this District and elsewhere, the claims of the '220 Patent are directed to unpatentable naturally occurring subject matter, phenomena, and/or relationships, and any additional elements in the claims are merely well-understood, routine, or conventional. Thus, the claims of the '220 Patent are unpatentable under 35 U.S.C. § 101.

127. For example, in another case pending in this District, *CareDX, Inc. et al. v. Natera, Inc.*, No. 19-cv-567 (D. Del.) ("CareDX"), Natera has alleged that the claims of the two patents-in-suit there—U.S. Patent Nos. 8,703,652 and 9,845,497—are unpatentable under 35 U.S.C. § 101. *See CareDX*, No. 19-cv-567, D.I. 9-10, 19 (Natera's Motion to Dismiss and Briefing Related Thereto), 63 (Natera's Objections to Report and Recommendation) (attached as Exhibits 1-4); *see also id.*, D.I. 86, 87 (Natera's Renewed Motion to Dismiss) (attached as Exhibits 7-8); *see also id.*, D.I. 100-02, 107-08 (Natera's Motion for Summary Judgment of Invalidity and Briefing Related Thereto) (attached as exhibits 9-13). The two patents asserted in CareDX claim priority to applications filed in 2009 and 2010, which is before the earliest possible priority date for the claims of the '220 Patent.

128. Similarly, in *Illumina, Inc. v. Natera, Inc.*, No. 18-cv-01662 (N.D. Cal.) (“*Illumina*”), Natera has alleged that the claims of U.S. Patent No. 9,493,831 are unpatentable under Section 101. *See Illumina*, No. 18-cv-01662, D.I. 24, 35 (Motion to Dismiss and Briefing Related Thereto) (attached as Exhibits 5-6). The patent asserted in *Illumina* claims priority to an application filed in 2010, which is before the earliest possible priority date for the claims of the ’220 Patent.

129. In this case, representative claim 1 of the ’220 Patent recites a “a method for amplifying and sequencing DNA” comprising (1) ligating adaptors to isolated cell-free DNA, (2) performing a first round of polymerase chain reaction (PCR), (3) performing a second, “nested” round of PCR that includes use of a sequencing tag, and (4) performing high-throughput sequencing to sequence the cell-free DNA.

130. But in *CareDX*, Natera itself acknowledged that cell-free DNA is a natural phenomenon, and alleged that amplification and sequencing methods, such as PCR and high throughput sequencing, were known and used in the art to detect and sequence cell-free DNA. *E.g., CareDX*, D.I. 10 at 12-19; D.I. 19 at 6-7; D.I. 63 at 3-5. And in *Illumina*, Natera also argued that cell-free DNA is “naturally occurring,” and the use of “well-known, routine, and conventional amplification techniques”—including nested PCR, and the use of primers with attached sequencing tags—to amplify and sequence the DNA is not patentable. *See Illumina*, No. 18-cv-01662, D.I. 24 at 2, 6-8; D.I. 35 at 2-9.

131. Thus, by Natera’s own admissions, the claims of the ’220 Patent are unpatentable under 35 U.S.C. § 101, and Natera should never have filed its Complaint against the Counterclaimants.

**Invalidity under 35 U.S.C. §§ 102 and 103**

132. The claims of the '220 Patent are invalid under 35 U.S.C. § 102 and/or § 103, in view of, for example, the following prior art, alone or in combination with additional prior art: Mir, with Siebert, Wang, Spertini, or Makarov, which disclose all elements of the '220 Patent claims. Natera disclosed Mir, Wang, Spertini, and Makarov as four of thousands of references during prosecution of the '220 Patent. Natera did not disclose Siebert to the USPTO during prosecution of the '220 Patent. Moreover, the '220 Patent is at least obvious under 35 U.S.C. § 103 given Natera's own admissions made in court filings in this District and elsewhere, representative examples of which are set forth above in paragraphs 126-31.

133. The '220 Patent is also not entitled to a priority date earlier than its filing date of January 15, 2020, because Natera's provisional applications and earlier-filed applications do not comply with the requirements of 35 U.S.C. § 112, as required by 35 U.S.C. §§ 119 and 120. The provisional applications and earlier-filed applications do not contain a written description of the claims of the '220 Patent or contain sufficient information to enable a person of ordinary skill in the art to which they pertain to practice the full scope of the claims of the '220 Patent. Indeed, none of the provisional applications or earlier-filed applications disclosed the claimed methods or sought claims corresponding to the claims of the '220 Patent, which recite processes that Natera did not invent.

134. Because the '220 Patent is not entitled to a priority date earlier than its filing date of January 15, 2020, it is invalid under 35 U.S.C. § 102 and/or § 103, in further view of, for example, the following prior art, alone or in combination with additional prior art: Hu or Murtaza, which disclose all elements of the '220 Patent claims. Hu and Murtaza were disclosed as two of thousands of references to the USPTO during prosecution of the '220 Patent.

135. The '220 patent is further invalid for failing to name the proper inventors under 35 U.S.C. § 102(f), as set forth above in paragraphs 354-88 of Defendants' answer.

**Invalidity under 35 U.S.C. § 112 and Improper Inventorship**

136. The claims of the '220 Patent are invalid under 35 U.S.C. § 112.

137. The claims of the '220 Patent lack written description support in the specification.

138. As an example, the specification of the '220 Patent does not disclose an embodiment or example corresponding to claim 1 of the '220 Patent and does not otherwise disclose that the named inventors of the '220 Patent were in possession of the alleged invention recited in the claims as of the priority date of the '220 Patent.

139. Indeed, prior to the filing of the '220 Patent application on January 15, 2020, Natera had never disclosed the claimed methods nor sought claims corresponding to the claims of the '220 Patent.

140. The specification also does not contain sufficient information to enable a person of ordinary skill in the art to which the patent pertains to practice the full scope of the claims of the '220 Patent.

141. The '220 Patent does not satisfy the requirements of 35 U.S.C. § 112 because the applicants for the '220 Patent did not themselves invent the subject matter sought to be patented—an independent ground for invalidating the patent.

**FOURTEENTH COUNTERCLAIM**  
**(Declaratory Judgment of Unenforceability Of The '220 Patent Due to Inequitable Conduct)**

142. The Counterclaimants reallege and incorporate its preliminary statement, and the allegations set forth in paragraphs 1-141 of these Counterclaims as if fully restated herein.

143. Defendants incorporate herein by reference the facts set forth with particularity in paragraphs 354-88 of their answer above. As alleged in the incorporated paragraphs, the '220 patent is unenforceable due to inequitable conduct.

#### **RESERVATION OF RIGHTS**

144. The Counterclaimants expressly reserve the right to assert any additional defenses or counterclaims that may now exist or in the future may be available based on discovery and further factual investigation in this case.

#### **DEMAND FOR JURY TRIAL**

145. The Counterclaimants hereby demand a trial by jury of all issues so triable in this action.

#### **PRAYER FOR RELIEF**

146. The Counterclaimants respectfully request this Court grant relief as follows:

A. Judgment that Natera's Second Amended Complaint in its entirety be dismissed with prejudice;

B. Judgment that Natera is entitled to nothing by its Second Amended Complaint, including that Natera is not entitled to an award of compensatory damages, attorneys' fees, costs, pre-judgment or post-judgment interest under 35 U.S.C. §§ 284 or 285, or any applicable law;

C. Denial of any and all of Natera's requests for injunctive relief;

D. Judgment that the Counterclaimants have not infringed, and are not infringing, any valid and enforceable claim of the Asserted Patents by its sale of LIQUIDPlex™, FusionPlex®, or VariantPlex® for research use only;

E. Judgment that the claims of the Asserted Patents are invalid;

F. Judgment that Natera and/or any of its successors and attorneys, and all persons in active concert or participation with any of them, are enjoined from directly or indirectly asserting infringement or instituting any further action for infringement of the Asserted Patents against ArcherDX, or any of ArcherDX's customers, end-users, agents, suppliers, contractors, consultants, successors, and assigns;

G. Judgment that the Asserted Patents are unenforceable;

H. Order that this case is "exceptional" pursuant to 35 U.S.C. § 285 entitling ArcherDX to an award of its reasonable and necessary attorneys' fees, expenses, and costs, and prejudgment and post-judgment interest thereon;

I. Order awarding the Counterclaimants their costs incurred in this action; and

J. Grant to the Counterclaimants such other and further relief as the Court deems just and proper.



Dated: September 1, 2021

Respectfully submitted,

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# **EXHIBIT 1**

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

CAREDX, INC. and THE BOARD OF	)	
TRUSTEES OF THE LELAND STANFORD	)	
JUNIOR UNIVERSITY,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	C.A. No. 19-567 (CFC)
	)	
NATERA, INC.,	)	
	)	
Defendant.	)	

**DEFENDANT NATERA, INC.'S MOTION TO DISMISS  
PURSUANT TO FEDERAL RULE OF CIVIL PROCEDURE 12(b)(6)**

Pursuant to Federal Rule of Civil Procedure 12(b)(6), Defendant Natera, Inc. moves to dismiss all counts of the Complaint for failure to state a claim upon which relief can be granted.

The grounds for this motion are set forth in Defendant's Opening Brief, submitted herewith.

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*/s/ Derek J. Fahnestock*

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May 16, 2019

**CERTIFICATE OF SERVICE**

I hereby certify that on May 16, 2019, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on May 16, 2019, upon the following in the manner indicated:

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# **EXHIBIT 2**

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

CAREDX, INC. and THE BOARD OF	)	
TRUSTEES OF THE LELAND STANFORD	)	
JUNIOR UNIVERSITY,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	C.A. No. 19-567 (CFC)
	)	
NATERA, INC.,	)	
	)	
Defendant.	)	

**DEFENDANT NATERA INC.'S OPENING BRIEF IN SUPPORT OF ITS MOTION TO  
DISMISS PURSUANT TO FEDERAL RULE OF CIVIL PROCEDURE 12(b)(6)**

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## I. NATURE AND STAGE OF THE PROCEEDINGS

Plaintiffs CareDx, Inc. (“CareDx”) and The Board Of Trustees Of The Leland Stanford Junior University (“Stanford,” and collectively with CareDx “Plaintiffs”) filed their complaint on March 26, 2019 (the “Complaint”). D.I. 1. Pursuant to Fed. R. Civ. P. 12(b)(6), Natera files this motion to dismiss the Complaint for failure to state a claim upon which relief can be granted.

## II. SUMMARY OF THE ARGUMENT

Plaintiffs allege that Natera’s Kidney Transplant Rejection Test (“Kidney Test”) infringes U.S. Patent Nos. 9,845,497 (“‘497 patent”), Ex. A,<sup>1</sup> and 8,703,652 (“‘652 patent”), Ex. B (the “Patents”).<sup>2</sup> But Plaintiffs cannot show they are entitled to relief for at least two reasons.

First, the claims of the Patents are invalid because they claim unpatentable subject matter under 35 U.S.C. § 101. It is well-settled that “laws of nature, natural phenomena, and abstract ideas are not patentable.” *Mayo Collaborative Servs. v. Prometheus Labs, Inc.*, 566 U.S. 66, 70 (2012) (internal quotation marks and citations omitted). Yet the Patents rest entirely on observing natural phenomena inherent to organ transplants: the presence of an organ donor’s nucleic acids (such as DNA) in the transplant recipient’s circulation (such as blood), and a correlation of that presence to rejection of the transplanted organ by the recipient’s body. They claim nothing more than the detection and use of these phenomena by conventional methods well known in the art, which is not patentable. The claims begin and end with nucleic acids and their correlation to disease, both of which are natural phenomena, and they therefore claim ineligible subject matter. *See Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1376 (Fed. Cir. 2015) (“The method therefore begins and ends with a natural phenomenon. Thus, the claims are directed to matter that is naturally occurring.”).

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<sup>1</sup> Citations to “Ex.” refer to exhibits to the Declaration of Sandra L. Haberny, filed herewith.

<sup>2</sup> The Patents have a common written description, and one independent claim each.

Second, Plaintiffs’ contention that Natera’s Kidney Test infringes the ’652 patent should be dismissed under *Ashcroft v. Iqbal*, 556 U.S. 662 (2009), and *Bell Atlantic Corp. v. Twombly*, 550 U.S. 544 (2007), for failure to state facts plausibly entitling them to relief. Specifically, Plaintiffs fail to allege facts plausibly showing that Natera’s Kidney Test practices a critical element of the sole independent claim (claim 1) of the ’652 patent. Claim 1 element (d) requires that “sensitivity of the method is greater than 56% **compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV)**.” See Ex. B, at 27:67-28:40.<sup>3</sup> This requirement was added during prosecution to overcome prior art, and therefore limited the scope of the claims. Yet, Plaintiffs now accuse Natera of using technologies within the scope of that prior art to support their infringement claims. The complaint recites no facts showing any **comparison** of the sensitivity of Natera’s ***Kidney Test*** to anything at all—much less a literal comparison to the claimed method for surveillance of a ***cardiac*** disorder. Nor can Plaintiffs ever show this because Natera’s Kidney Test does not involve any such comparison. Plaintiffs thus have not made a plausible showing of literal infringement, and prosecution history estoppel bars them from arguing Natera infringes under a doctrine of equivalents theory. The infringement claim likewise fails.

These deficiencies cannot be cured through amendment. Plaintiffs cannot show entitlement to relief, and the complaint should be dismissed with prejudice in its entirety.

### III. STATEMENT OF FACTS

#### A. The Claims Of The Patents

Independent claim 1 of the ’652 patent, Ex. B, at 27:38-29:20, recites the following steps:

1. A method for detecting transplant rejection, graft dysfunction, or organ failure, the method comprising:

(a) ***providing a sample comprising cell-free nucleic acids*** from a subject who has received a transplant from a donor;

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<sup>3</sup> All emphases are added unless otherwise noted.

(b) **obtaining a genotype** of donor-specific polymorphisms or a genotype of subject-specific polymorphisms, or obtaining both a genotype of donor-specific polymorphisms and subject-specific polymorphisms, **to establish a polymorphism profile for detecting donor cell-free nucleic acids**, wherein at least one single nucleotide polymorphism (SNP) is homozygous for the subject if the genotype comprises subject-specific polymorphisms comprising SNPs;

(c) **multiplex sequencing** of the cell-free nucleic acids in the sample **followed by analysis of the sequencing results using the polymorphism profile** to detect donor cell-free nucleic acids and subject cell-free nucleic acids; and

(d) **diagnosing, predicting, or monitoring a transplant status or outcome** of the subject who has received the transplant **by determining a quantity of the donor cell-free nucleic acids** based on the detection of the donor cell-free nucleic acids and subject cell-free nucleic acids by the multiplexed sequencing, wherein an **increase in the quantity of the donor cell-free nucleic acids over time is indicative of transplant rejection, graft dysfunction or organ failure**, and wherein **sensitivity of the method is greater than 56% compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV)**.

Independent claim 1 of the '497 patent, Ex. A, at 28:1-30:61, recites the following steps:

1. A method of detecting donor-specific circulating cell-free nucleic acids in a solid organ transplant recipient, the method comprising:

(a) **genotyping a solid organ transplant donor** to obtain a single nucleotide polymorphism (SNP) profile of the solid organ transplant donor;

(b) **genotyping a solid organ transplant recipient** to obtain a SNP profile of the solid organ transplant recipient, wherein the solid organ transplant recipient is selected from the group consisting of: a kidney transplant, a heart transplant, a liver transplant, a pancreas transplant, a lung transplant, a skin transplant, and any combination thereof;

(c) **obtaining a biological sample from the solid organ transplant recipient** after the solid organ transplant recipient has received the solid organ transplant from the solid organ transplant donor, wherein the biological sample is selected from the group consisting of blood, serum and plasma, and wherein the biological sample comprises circulating cell-free nucleic acids from the solid organ transplant; and

(d) **determining an amount of donor-specific circulating cell-free nucleic acids from the solid organ transplant in the biological sample** by detecting a homozygous or a heterozygous SNP within the donor-specific circulating cell-free nucleic acids from the solid organ transplant in at least one assay, **wherein the at least one assay comprises high-throughput sequencing or digital polymerase chain reaction (dPCR)**, and wherein the at least one assay detects the donor-specific circulating cell-

free nucleic acids from the solid organ transplant *when the donor-specific circulating cell-free nucleic acids make up at least 0.03% of the total circulating cell-free nucleic acids* in the biological sample.

## **B. The Claims Of The Patents Are Directed To Natural Phenomena**

The Patents are directed to analyzing naturally occurring biological molecules (here, nucleic acids) in organ transplant recipients. The pertinent properties of nucleic acids are well-accepted scientific principles. *See, e.g., Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 580-82 (2013). Nucleic acids, such as deoxyribonucleic acid (“DNA”), typically exist inside of cells. *Id.* at 582. They encode genetic information necessary for building and maintaining cells and making them function. The building blocks of nucleic acids, called “nucleotides,” store genetic information in the form of ordered “sequences,” which describe unique series of nucleotide bases that make up an individual’s genes. *Id.* at 580-81. The genes in aggregate comprise the individual’s “genome,” and naturally occurring variations in the sequences differentiate individuals. *Id.* The Patents do not alter these inherent principles in any way.

The common disclosure of the Patents acknowledges that nucleic acids can be found outside cells, and that such “cell-free” nucleic acids (e.g., in circulating blood) are a well-known natural phenomenon. The Patents also acknowledge that it is well-known that cell-free nucleic acids are the product of diseases involving death, or “apoptosis,” of cells containing the nucleic acids, and that this occurs in cancer and in transplant rejection. Ex. B, at 6:57-67 (“Circulating, or cell-free, DNA was first detected in human blood plasma in 1948. ... Since then, its connection to disease has been established in several areas. ... Studies reveal that much of the circulating nucleic acids in blood arise from necrotic or apoptotic cells ... and greatly elevated levels of nucleic acids from apoptosis is observed in diseases such as cancer. ...”); 7:40-46 (“[A]s cell-free DNA or RNA often arises from apoptotic cells, the relative amount of donor-specific sequences in circulating nucleic acids should provide a predictive measure of on-coming organ failure in transplant patients...”). As the common

disclosure makes clear, “[i]n all these applications of circulating nucleic acids, the presence of sequences differing from a patient’s normal genotype has been used to detect disease.” *Id.* at 7:30-32. Thus, detecting nucleic acids that originated from the donor organ in a transplant recipient’s circulation is simply a matter of observing a natural phenomenon: the presence of nucleic acids different from those normally present in the recipient’s circulation. *See also id.* at 6:67-7:16; 7:19-29; 7:40-46; 8:18-21.

The Patents recount various ways that nucleic acid sequences of a transplant donor and recipient may differ, including by what are called “polymorphisms.” According to the Patents, “[a] polymorphism refers to the occurrence of two or more genetically determined alternative sequences or alleles in a population.” *Id.* at 11:24-26. The Patents disclose that “[a] polymorphism between two nucleic acids can occur *naturally*....” *Id.* at 11:39-44. The Patents also disclose various types of polymorphisms, including “single nucleotide polymorphisms (SNP’s),” which are DNA sequences that differ between individuals at a single nucleotide position.

The Patents cite numerous references from the 1990’s disclosing that “as cell-free DNA or RNA often arises from apoptotic (*i.e.*, dying) cells, the relative amount of donor-specific sequences in circulating nucleic acids should provide a predictive measure of on-coming [sic] organ failure in transplant patients....” *Id.* at 7:41-46. The Patents also provide examples of how such techniques could be used to make diagnoses based upon donor-derived cell-free nucleic acids in a transplant recipient’s circulation. *Id.* at 7:47-8:21. The Patents explain that “for heart transplant patients, donor-derived DNA present in [blood] plasma can serve as a potential marker for the onset of organ failure.” *Id.* at 8:18-21.

The Patents acknowledge that donor-specific cell-free nucleic acids in a transplant recipient’s circulation and their correlation to transplant rejection are Nature’s handiwork.

### C. Amendment To Add Sensitivity Limitation

The '652 patent describes monitoring transplant rejection, and discloses only one application of this – monitoring a heart condition called cardiac allograft vasculopathy (“CAV”). Ex. B, at 5:54-6:55; *see also id.* at 6:1-3. The '652 patent discloses that “[c]urrent surveillance methods for CAV lack adequate sensitivity or require invasive procedures and the most commonly applied method, coronary angiography, lacks sensitivity.” *Id.* at 6:8-12. The '652 patent incorporates by reference, *id.* at 3:3-7, a publication by Kobashigawa, J.A., *et al.* (“Kobashigawa”), which describes these “current surveillance methods,” particularly the “most commonly applied method, coronary angiography,” *id.* at 6:8-12. Kobashigawa explains that this technique is an “intravascular ultrasound” that “is an invasive procedure that detects thickening in the walls of the coronary arteries,” and “provides a sonar image of intimal and media thickness.” Ex. E, at 1532.

As issued, claim 1(d) of the '652 patent recites, in pertinent part, “wherein sensitivity of the method is greater than 56% compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV).” Ex. B, at 27:67-28:40. The patent Examiner added the clause “*compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV)*” to then-claim 36 (which became claim 1), following an interview with the applicant, in order to overcome prior art and secure allowance. Ex. F, at 4-5; Ex. G, at 2 (showing prior claim language lacking amendment). The Examiner’s “Reasons for Allowance,” Ex. F, at 3, state:

By amendment to the claims, Applicant has persuaded the Examiner that the prior art . . . alone or in combination, do not teach or disclose a method for detecting transplant rejection, graft dysfunction, or organ failure . . . wherein the sensitivity of the method *is greater than 56% compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV)*.

### D. Natera’s Accused Kidney Test

Plaintiffs allege that Natera is infringing their Patents by “market[ing] and sell[ing] a Kidney Transplant Rejection Test.” D.I. 1, at ¶ 10. Pertinent here, Plaintiffs allege that Natera’s Kidney Test



infringes '652 patent claim element 1(d), which requires that “sensitivity of the method is greater than 56% *compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV).*” Ex. B, at 27:67-28:40. But the Complaint makes no allegation of any comparison to the sensitivity anything, much less that of a surveillance method for a heart condition, such as CAV. At most, the complaint alleges stand-alone measures of Natera’s Kidney Test’s sensitivity for detecting kidney transplant rejection. D.I. 1, at ¶ 24; *id.*, Ex. 8, at 7-8.

#### IV. LEGAL STANDARD

##### A. Natural Phenomena Are Not Patentable

“[L]aws of nature, natural phenomena, and abstract ideas are not patentable.” *Mayo*, 566 U.S. at 70. “The inventive concept [of a claim] cannot be furnished by the unpatentable law of nature (or natural phenomenon or abstract idea) itself.” *Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1376 (Fed. Cir. 2016). “[S]imply appending conventional steps, specified at a high level of generality, to laws of nature, natural phenomena, and abstract ideas cannot make those laws, phenomena, and ideas patentable.” *Mayo*, 566 U.S. at 82. And “[t]he prohibition against patenting abstract ideas cannot be circumvented by attempting to limit the use of the [abstract idea] to a particular technological environment or adding insignificant post solution activity.” *Id.* at 73. Only “innovative” or “inventive” uses of natural phenomena are afforded patent protection. *Myriad*, 569 U.S. at 595 (“Had *Myriad* created an innovative method of manipulating genes while searching for the [natural] genes, it could possibly have sought a method patent.”); *Parker v. Flook*, 437 U.S. 584, 594 (1978) (“[A]n inventive application of the principle may be patented.”).

According to the *Mayo* framework, patent claims are ineligible for protection if they: (1) are directed to a patent-ineligible concept and (2) fail to recite additional elements constituting an inventive concept “sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself.” *Mayo*, 566 U.S. at 72-73, 77-80; *Ariosa*, 788 F.3d at 1375.



Importantly, “[t]he inventive concept necessary at step two of the *Mayo/Alice* analysis cannot be furnished by the unpatentable law of nature (or natural phenomenon or abstract idea) itself. That is, under the *Mayo/Alice* framework, a claim directed to a newly discovered law of nature (or natural phenomenon or abstract idea) cannot rely on the novelty of that discovery for the inventive concept necessary for patent eligibility.” *Genetic Techs.*, 818 F.3d at 1376.

Patentability under 35 U.S.C. § 101 is a threshold legal issue that must be answered early in a case. *Bilski v. Kappos*, 561 U.S. 593, 602 (2010)); *see also Ultramercial, Inc. v. Hulu, LLC*, 772 F.3d 709, 717, 718 (Fed. Cir. 2014) (Mayer, J., concurring) (“[W]hether claims meet the demands of 35 U.S.C. § 101 is a threshold question, one that must be addressed at the outset of litigation,” which will have “a number of salutary effects.”). A § 101 inquiry is properly raised at the pleadings stage if it is apparent from the face of the patent that the asserted claims are not directed to eligible subject matter. *See Berkheimer v. HP Inc.*, 881 F.3d 1360, 1368 (Fed. Cir. 2018) (“Patent eligibility has in many cases been resolved on motions to dismiss.”); *Cleveland Clinic Found. v. True Health Diagnostics LLC*, 859 F.3d 1352, 1360 (Fed. Cir. 2017). Moreover, claim construction is not required to conduct a § 101 analysis. *Genetic Techs.*, 818 F.3d at 1374. And a court need not individually address claims not asserted or identified by the non-moving party if the court identifies a representative claim and “all the claims are substantially similar and linked to the same abstract idea.” *Content Extraction & Transmission LLC v. Wells Fargo Bank, Nat. Ass’n*, 776 F.3d 1343, 1348 (Fed. Cir. 2014) (internal quotation marks omitted).

## **B. Claims Must Be Dismissed If Not Supported by Plausible Facts**

“[A] plaintiff’s obligation to provide the ‘grounds’ of his ‘entitle[ment] to relief’ requires more than labels and conclusions, and a formulaic recitation of the elements of a cause of action will not do.” *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 555 (2007); *see Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009). “[A] complaint must do more than allege the plaintiff’s entitlement to relief. A

complaint has to ‘show’ such an entitlement with its facts,” *Fowler v. UPMC Shadyside*, 578 F.3d 203, 211 (3d Cir. 2009), which must rise “above the speculative level.” *Twombly*, 550 U.S. at 555. To plead patent infringement, a complaint must allege facts making it plausible that the accused instrumentality “practice[s] each of the limitations found in the [] asserted claims.” *See, e.g., N. Star Innovations, Inc. v. Micron Tech., Inc.*, 2017 WL 5501489, at \*1-2 (D. Del. Nov. 16, 2017).

### **C. Prosecution History Estoppel Bars Use Of Doctrine Of Equivalents**

A party may allege patent infringement either literally or under the doctrine of equivalents (“DOE”). *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 35 (1997). DOE applies if either: the accused product performs “substantially the same function in substantially the same way to obtain the same result” or the accused product or process is not substantially different from what is patented (“the insubstantial differences test”). *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, 857 F.3d 858, 866 (Fed. Cir. 2017). Because DOE “can create substantial uncertainty about where the patent monopoly ends,” the Supreme Court has “acknowledged that competitors may rely on the prosecution history, the public record of the patent proceedings” for clarity. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 727 (2002).

Accordingly, prosecution history estoppel is invoked where a patentee makes a narrowing amendment to secure allowance during prosecution. *Id.* at 736. Where the amendment “narrow[s] [patentee’s] claims, this prosecution history estops [patentee] from later arguing that the subject matter covered by the original, broader claim was nothing more than an equivalent.” *Id.* at 727. Narrowing amendments bar a patentee from asserting amended limitations are infringed under DOE by practicing the subject matter an amendment was made to avoid. *Id.* Pertinent here, estoppel applies with particular force where “the examiner’s Reasons for Allowance make clear that the examiner and the applicant understood that the invention requires [the added limitation].” *ACCO Brands, Inc. v. Micro Sec. Devices, Inc.*, 346 F.3d 1075, 1079 (Fed. Cir. 2003).

## V. ARGUMENT

### A. The Claims Of The Patents Are Invalid Under § 101

#### 1. The Focus Of The Asserted Claims Is Entirely On Natural Phenomena

“For an application of an abstract idea to satisfy step one [of the *Mayo* framework], the claim’s focus must be on something other than the abstract idea itself.” *BSG Tech LLC v. Buyseasons, Inc.*, 2018 WL 3862646, at \*4 (Fed. Cir. Aug. 15, 2018). The asserted claims here are focused on nothing other than natural phenomena stemming from donor-specific cell-free nucleic acids circulating in a transplant recipient’s body. Ex. B, at 6:61-64 (“Studies reveal that much of the circulating nucleic acids in blood arise from necrotic or apoptotic cells...”); 7:40-46 (“[A]s cell-free DNA or RNA often arises from apoptotic cells, the relative amount of donor-specific sequences in circulating nucleic acids should provide a predictive measure of on-coming organ failure in transplant patients...”); *see also* section III.B above. These cell-free nucleic acids appear as the natural result of a transplanted organ’s cells dying (*i.e.*, apoptosis), which happens increasingly when there is organ rejection, dysfunction, or failure. *Id.* As such, detecting or correlating the presence of a donor’s cell-free nucleic acids in the transplant recipient’s circulation to transplant status is nothing more than observing a natural phenomena.

The asserted claims here begin and end with those natural phenomena. *Ariosa*, 788 F.3d at 1376 (“The method therefore begins and ends with a natural phenomenon. Thus, the claims are directed to matter that is naturally occurring.”). For example, ’652 patent claim 1 element (a) starts with “a sample comprising cell-free nucleic acids from a subject who has received a transplant,” and element (d) ends with “diagnosing, predicting, or monitoring a transplant status or outcome of the subject ... by determining a quantity of the donor cell-free nucleic acids based on the detection of the donor cell-free nucleic acids and subject cell-free nucleic acids...” in the sample. Ex. B, at 27:41-43; 27:59-63. For the ’497 patent, claim 1 preamble starts with “detecting donor-specific

circulating cell-free nucleic acids in a solid organ transplant recipient,” and ends in element (d) with “determining an amount of donor-specific circulating cell-free nucleic acids from the solid organ transplant in the biological sample...” Ex. A, at 28:2-3; 28:24-26; 28:26-29.

These claims parallel those found ineligible in *Mayo*, *Genetic Techs.*, and *Ariosa*.<sup>4</sup> For example, in *Mayo*, the Supreme Court found the claims ineligible because they “set forth laws of nature - namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of [] drug will prove ineffective or cause harm.” *Mayo*, 566 U.S. at 77. Here the ’652 patent claims likewise merely recite relationships between amounts of circulating donor-specific cell-free nucleic acids in the organ recipient and corresponding transplant status.

Similarly, in *Ariosa*, the alleged invention was only that “paternally inherited [cell-free fetal DNA] is to be found in maternal blood (using established detection techniques).” *Genetic Techs.*, 818 F.3d at 1376 (referencing *Ariosa*). Again, the ’497 patent claims are no different, reciting only established techniques to detect donor-specific cell-free nucleic acids in the transplant recipient. And like here, the *Ariosa* inventors applied only “a combination of known laboratory techniques” to amplify and detect paternally inherited cell-free fetal DNA already in the mother’s blood. *Ariosa*, 788 F.3d at 1373. As the Court should here, in *Ariosa* the Federal Circuit held the claims were invalid because they were merely “directed to detecting the presence of a naturally occurring thing or a natural phenomenon, [cell-free fetal DNA] in maternal plasma or serum.” *Id.* at 1376; *see also Genetic Techs.* 818 F.3d at 1375-76 (finding that, like here, “the claims are directed to matter that is naturally occurring,” and the method involved “no creation or alteration of DNA sequences”).

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<sup>4</sup> *See also Cleveland Clinic*, 859 F.3d at 1361 (detecting enzyme in order to diagnose cardiovascular risk); *23andMe, Inc. v. Ancestry.com DNA, LLC*, 356 F. Supp. 3d 889, 904 (N.D. Cal. 2018) (detecting correlation that exists in nature).

## 2. The Additional Elements Do Not Add Enough For Patentability

The asserted claims add no inventive concept “sufficient to ensure that the patent in practice amounts to **significantly** more than a patent upon the natural law itself.” *Mayo*, 566 U.S. at 73. To the contrary, like the claims found ineligible in *Mayo*, “the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field.” *Id.* That is insufficient to confer patentability. *See, e.g., Ariosa*, 788 F.3d at 1373, 1377-78; *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755, 764-65 (Fed. Cir. 2014).

For the Court’s convenience, Ex. C includes a table identifying, for each claim element, excerpts from the Patents disclosing the routine and conventional nature of the techniques recited. These disclosures are also summarized below.

### (a) The Independent Claims

Far from providing any new teachings on how to perform the recited steps, novelty in any of the techniques recited, or unconventional combinations thereof, the Patents expressly describe only “conventional” techniques that were and are “known in the art” to carry out the claimed methods. At the outset, the Patents state:

The practice of the present invention employs, unless otherwise indicated, **conventional techniques** of immunology, biochemistry, chemistry, molecular biology, microbiology, cell biology, genomics and recombinant DNA, **which are within the skill of the art.**

Ex. B, at 5:36-48 (numerous references omitted). The Patents also identify each and every specific step recited in the claims as “conventional.”

For example, as to the steps of “providing a sample” and “obtaining a biological sample” from the transplant recipient (’652 element 1(a) and ’497 element 1(c), respectively), the common disclosure states that “[t]o obtain a blood sample, any **technique known in the art** may be used...”

Ex. B, at 10:11-12; *id.* at 1:14-17; 6:57-67; 9:4-14; 10:7-10. Similarly, for the “**genotype**” or “**genotyping**” to establish a polymorphism or SNP “profile” (’652 element 1(b) and ’497 elements 1(a)-(b), respectively), the Patents disclose that “[g]enotyping of the transplant donor and/or the transplant recipient may be performed **by any suitable method known in the art** including those described herein such as sequencing ... or PCR.” *Id.* at 20:31-37; 13:51-67 (“using **existing genotyping platforms known in the art**”); 20:31-51; 26:38-41.

The “multiplex sequencing” and “high-throughput sequencing or digital polymerase chain reaction (dPCR)” of ’652 element 1(c) and ’497 element 1(d), respectively, are disclosed as techniques that “can be performed by sequencing such as whole genome sequencing or exome sequencing,” and also “can be accomplished through classic Sanger sequencing methods which are **well known in the art.**” *Id.* at 15:2-8. The Patents further disclose additional techniques well known in the art, including commercial technologies, *id.* at 15:22-52, and others described in the literature, *id.* at 15:53-17:14; *see also id.* at 7:23-28; 9:8-14; 14:58-67; 15:22-17:14; 21:5-8.

The methods for “diagnosing, predicting, or monitoring a transplant status or outcome” by “determining a quantity of the donor cell-free nucleic acids” (’652 element 1(d)), and “determining an amount of donor-specific circulating cell-free nucleic acid” (’497 element 1(d)) also are routine. The Patents disclose that “[d]etection, identification, and/or quantification of the donor-specific markers (e.g., polymorphic markers such as SNPs) can be performed using [numerous techniques]... as well as other methods **known in the art including the methods described herein.**” *Id.* at 9:8-14; 18:56-19:2 (“Methods for quantifying nucleic acids **are known in the art...**”); 17:41-18:53; 21:5-9 (“The presence or absence of one or more nucleic acids from the transplant donor in the transplant recipient may be determined by any suitable method **known in the art including those described herein** such as sequencing, nucleic acid arrays or PCR.”).

The recitation in '652 element 1(d) that “an increase in the quantity of the donor cell-free nucleic acids over time is indicative of” a transplant-related disorder refers to nothing more than the natural phenomenon itself. *See, e.g., id.* at 7:40-46. As to the final '652 patent limitation that “sensitivity of the method is greater than 56% compared to sensitivity of current surveillance methods for ... CAV,” assuming *arguendo* that this is not indefinite for purposes of this Motion only, any sensitivity would have to be an inherent feature of the conventional methods used to perform the claim. The patent discloses that as a general matter, “[t]he invention provides methods that [are] sensitive and specific,” and describes all embodiments as having sensitivity of at least 56%. *Id.* at 23:31-44; *see also id.* at 5:36-40. The patent also discloses, among other standard techniques, sequencing using the commercially available “Illumina Genome Analyzer,” for which “[h]igher sensitivity can be achieved simply by sequencing more molecules, i.e., using more channels,” *id.* at 17:12-13, and “sequencing error rate,” which “also affects the sensitivity of this technique,” can be “systematically lower[ed] ... by resequencing the sample template multiple times, as has been demonstrated by Helicos BioSciences,” another commercial provider of conventional sequencers. *Id.* at 17:14-15; 17:22-25. Hence, there is no assertion or evidence that these techniques – or sensitivities that naturally result from their use – is unconventional or new.

Finally, '497 patent element 1(d), reciting “wherein the at least one assay detects the donor-specific circulating cell-free nucleic acids from the solid organ transplant when the donor-specific circulating cell-free nucleic acids make up at least 0.03% of the total circulating cell-free nucleic acids in the biological sample,” Ex. A, at 29:1-5, again states no more than a natural phenomenon: presence of a certain fraction of donor-specific cell-free nucleic acids in a transplant recipient’s circulation. The Patents ascribe nothing unconventional to detection of this by standard techniques. Instead, the Patents state that the commercial Illumina Genome Analyzer is capable of “detecting



donor molecules when the donor fraction is as low as 0.03%.” Ex. B at 17:1-3; 17:7-11.

In sum, the Patents do not contend that any of the claimed techniques were new or unconventional, or that there was any challenge associated with using them. In fact, the Patents admit over and over that their techniques are routine, conventional, and well-known.

### (b) The Dependent Claims

The Complaint does not allege infringement of any dependent claims of the Patents. Nevertheless, the dependent claims also merely append conventional techniques to natural phenomena, and are thus also directed to unpatentable subject matter.

Claims 2 and 11 of the ’652 patent, *id.*, at 28:41-47; 29:5-7, and claim 24 of the ’497 patent, Ex. A, at 30:22-24, recite different types of “polymorphisms” assessed in the “polymorphism profile[s]” established during the “genotyp[ing]” step in the respective independent claims. Setting aside the fact that polymorphisms are naturally occurring genetic differences, Ex. B, at 11:24-26, the Patents (as discussed above) disclose that “[g]enotyping of the transplant donor and/or the transplant recipient” to identify these naturally occurring polymorphisms “may be performed by any *suitable method known in the art including those described herein.*” *Id.* at 20:31-33. The Patents further disclose establishing a profile comprising the recited types of polymorphisms. *Id.* at 20:42-51. But the patents do not describe these techniques as unconventional or new.

Claims 6, 17, 18, and 25 of the ’497 patent, Ex. A, at 29:17-18; 29:57-59; 30:25-28, recite detecting and analyzing numbers of single nucleotide polymorphisms (SNPs)<sup>5</sup> that are homozygous or heterozygous, or occur at different frequencies in the population. These polymorphisms again are genetic variances that occur naturally, *id.* at 11:22-33, and the claimed methods for detecting them

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<sup>5</sup> An individual naturally has a set of genes inherited from its mother, and another from its father. An individual is “homozygous” at a SNP locus when the nucleotide sequences it inherited from mother and father are the same there. An individual is “heterozygous” at a SNP locus when the sequences inherited from mother and father differ there. This, also, is a natural phenomenon.



are “known in the art,” Ex. B, at 20:31-33; 20:52-63. The patent also discloses commercial products for this, *id.* at 13:41-67, wherein “[c]ompanies ... currently offer both standard and custom-designed TaqMan probe sets for SNP genotyping...,” and “[w]ith such a large pool of potential SNPs to choose from, a usable subset of existing or custom probes can be selected to serve as the probe set for any donor/recipient pair.” *Id.* at 13:58-67.

Claim 26 of the ’497 patent recites “mapping” nucleic acids detected from the sample to a genome sequence of the transplant donor. Ex. A, at 30:29-33. The Patents again concede that this is known in the art, incorporating by reference publications describing it. Ex. B, at Page 2, References Cited (“Fan et al., Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood, *Proc Natl Acad Sci USA* (Oct. 2008), 105(42):16266-71 ...”); 3:3-7; 18:12-14; Ex. D (incorporated Fan publication) at 16266 (describing mapping techniques).

Claims 15 and 16 of the ’497 patent recite performing the “genotyping” step prior to, or simultaneously with, “determining” an amount of donor-specific cell-free nucleic acids. Ex. A, at 29:47-55. This step is conventional and routine when detecting disease, as the Patents admit. *E.g.*, Ex. B, at 7:30-32; 20:31-34. The Patents disclose performing “genotyping” before “determining,” for example, where “[b]oth the donor and recipient will be genotyped prior to transplantation,” but this is a routine medical practice. *Id.* at 13:2-3. And the patent further describes performing them simultaneously as part of genotyping methods “known in the art.” *Id.* at 13:15-17.

Claims 3 and 12-16 of the ’652 patent, *id.* at 28:49-50; 29:8-20, and claims 2, 9, 12-14, 27, and 28 of the ’497 patent, Ex. A, at 29:6-7; 29:25-26; 29:34-46, 30:34-37, recite types of transplants and samples (bodily fluids or nucleic acids) from which the cell-free nucleic acids are obtained. According the Patents, this too is standard and conventional. Ex. B, at 1:14-19; 2:13-16; 6:57-67; 9:4-14; 10:11-12; 13:21-28. And the recitation of nucleic acids (DNA or RNA) as present in various

bodily fluids is, again, merely a recitation of the natural phenomenon itself.

Claims 4-6, and 10 of the '652 patent, *id.* at 28:51-57; 29:1-4, and claims 3-5, 10, 11, and 30 of the '497 patent, Ex. A, at 29:8-16; 29:27-34; 30:42-45, recite standard techniques for sequencing, amplification, and using a computer. It further describes commercially-available techniques, inherent to them. The patent describes all of this as known in the art, and conventional. Ex. B, at 7:23-28; 9:8-14; 14:11-21; 14:55-67; 15:8-17; 39; 20:31-36; 20:52-56; 24:35-64.

Claims 19-23, and 31-33 of the '497 patent, Ex. A, at 30:1-21; 30:47-62, recite features of sensitivity and error rates inherent in the claims' recited routine techniques. The patent likewise describes these as part of the corresponding knowledge in the art. Ex. B, at 16:57-59; 17:1-11; 17:20-28; 23:31-34; 25:46-63; 26:48-55. And the limitations to percent of donor-specific cell-free nucleic acids present in a sample, again, simply refer to the natural phenomenon itself.

Finally, claims 7-9 of the '652 patent, *id.* at 28:58-67, and claims 7, 8, and 29 of the '497 patent, Ex. A, at 29:19-24; 30:38-41, recite therapeutic treatments. The Patents similarly describe these as routine, generally practiced techniques. Ex. B, at 4:14-17; *id.* at 4:36-38.

Like the independent claims, apart from natural phenomena, the Patents ascribe nothing new to any of the techniques recited to perform the methods in the dependent claims.

**(c) The Claims Append Only Conventional Techniques Known In The Art To The Recited Natural Phenomena**

As explained above, the claims of the Patents are directed to natural phenomena: donor-specific cell-free nucleic acids in the circulation of an organ transplant recipient, and the relationship of the donor-specific cell-free nucleic acids to organ rejection or failure. Ex. B., at 7:40-46; 8:18-21; section III.B above. The asserted claims require only that these donor-specific cell-free nucleic acids be detected ('497 patent), or quantified to diagnose, predict, or monitor a transplant status or outcome ('652 patent). But the Patents identify nothing novel about the techniques recited to do so.

As in *Mayo*, “the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field.” 566 U.S. at 73; *see also Genetic Techs.*, 818 F.3d at 1376 (“The inventive concept ... cannot be furnished by the unpatentable law of nature (or natural phenomenon or abstract idea) itself.”). Nothing in the Patents suggests that those additional steps – or the recited combinations of them – are inventive in any way.

Here, too, this case is analogous to *Genetic Techs.* and *Ariosa*. In both cases, the Federal Circuit held that various “physical steps” such as the “physical steps of DNA amplification and analysis of the amplified DNA,” and “PCR to amplify and detect [the cell-free DNA]” were all well-understood and conventional—much like the physical steps of PCR/amplification, sequencing, and others here. *See Genetic Techs.*, 818 F.3d at 1377-78; *Ariosa*, 788 F.3d at 1377. Also instructive is the Federal Circuit’s decision in *In re BRCA*, in which the court concluded that the claims, directed to the abstract idea of comparing various DNA sequences, were not saved by the recitation of limitations that did “nothing more than spell out what practitioners already knew—how to compare gene sequences using routine, ordinary techniques,” such as “detecting,” “amplification,” and “sequencing.” *In re BRCAI*, 774 F.3d at 764 (Fed. Cir. 2014). None of the steps in these cases conferred patent eligibility because they extracted and analyzed natural phenomena in known and conventional ways. The same is true in this case.

Here, the only potential novelty is the presence of circulating donor-specific cell-free nucleic acids in a transplant recipient and the correlation of them to transplant status. But even if these natural phenomena were newly discovered (which they are not) such discovery alone does not make observation of the phenomena using conventional techniques patentable. This is why, in *Ariosa*, the court evaluated whether it was “well-understood, routine, and conventional activity” to combine the

method steps to detect DNA in blood *generally*, not whether it was routine to apply those steps *to a sample of maternal cell-free DNA* (the natural phenomenon at issue there). *Ariosa*, 788 F.3d at 1377. The *Ariosa* court rejected the notion that the *application* of well-understood, routine processes to the newly discovered phenomenon rendered the claims patent eligible, concluding that looking at the claimed processes as a whole, “the only inventive component of the processes ... is to *apply those well-understood, routine processes to* paternally inherited [cell-free fetal DNA], *a natural phenomenon*.” *Id.* at 1375. The same principle applies here, only to a different natural phenomenon – donor-specific cell-free nucleic acids.

### **B. Plaintiffs’ Unsupported ’652 Patent Infringement Claim Must be Dismissed**

To allege a plausible claim for infringement of the ’652 patent, claim element 1(d) requires Plaintiffs to plead facts showing that in Natera’s Kidney Test, “sensitivity of the method is greater than 56% compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV).” *See, e.g., Twombly*, 550 U.S. at 555; *N. Star Innovations*, 2017 WL 5501489, at \*1 (granting motion to dismiss for failure to show infringement of every limitation). Plaintiffs have not alleged this, let alone pled facts that plausibly support an infringement claim for this limitation.

As explained in section III.C above, CAV refers to a condition that occurs in connection with *heart* transplants. This is unrelated to *kidney* transplant rejection, which is the subject of Natera’s Kidney Test. Exhibit 8 of the Complaint purports to be a claim chart demonstrating how Natera’s Kidney Test satisfies this claim element, but it does not allege any facts to show that the accused test’s sensitivity is *compared* to that of *then-current methods* for surveillance of the *specific CAV heart* condition recited in the claim. D.I. 1, Ex. 8, at 7-8.

As explained in section III.C above, the patent discloses only invasive imaging/ ultrasound, as the heart transplant-related measure against which to compare for this. But the complaint makes no allegation that sensitivity of the accused non-invasive method for counting cell-free DNA in

Natera’s Kidney Test compares to sensitivity of invasive CAV surveillance methods. Plaintiffs have not pled that Natera literally does this. Nor can they, because not only does it make no sense to compare a kidney transplant test to the monitoring of conditions specific to a transplanted heart, but Natera does not compare the sensitivity of its Kidney Test to *anything* when performing it. That is clear from the face of the Complaint—which references and attaches a Natera publication on which Plaintiffs base their allegations. D.I. 1, Ex. 8 at 7-8 (referencing *id.*, at Ex. 9). That publication does not include any comparison of sensitivity of the Natera Kidney Test to anything, much less methods for surveillance of CAV as recited in the ’652 patent claims. *Id.*, Ex. 9.

Plaintiffs cannot demonstrate infringement literally, nor can they attempt to capture scope beyond this literal limitation under DOE. As explained in section III.C above, the limitation was added by amendment to overcome prior art, and was a reason the examiner allowed the patent. Prosecution history estoppel bars Plaintiffs from now attempting to recapture this scope—which Stanford expressly disclaimed to obtain the patent—under DOE. *See, e.g., Festo*, 535 U.S. at 727. Here the bar applies with particular force, as the amendment was added to overcome a rejection based on references that use *sequencing* techniques just as Plaintiffs allege Natera’s Kidney Test practices. *See* Ex. F, at 2-3 of “Detailed Action”; Ex. G, at 5-6. Plaintiffs cannot be permitted to recapture the very scope they surrendered in exchange for securing a patent.

The comparison of sensitivity of the accused Kidney Test to that of surveillance methods for CAV is a critical limitation, made to overcome prior art, and required to obtain issuance of the patent. Plaintiffs have not alleged facts to plausibly show that Natera practices it literally, and they are barred from alleging it under DOE. Plaintiffs’ claim must be dismissed.

## VI. CONCLUSION

Natera requests that the Court dismiss the Complaint in its entirety with prejudice.

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May 16, 2019

**CERTIFICATE OF SERVICE**

I hereby certify that on May 16, 2019, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on May 16, 2019, upon the following in the manner indicated:

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# **EXHIBIT 3**



IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

CAREDX, INC. and THE BOARD OF	)	
TRUSTEES OF THE LELAND STANFORD	)	
JUNIOR UNIVERSITY,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	C.A. No. 19-567 (CFC)
	)	
NATERA, INC.,	)	
	)	
Defendant.	)	

**DEFENDANT NATERA INC.'S REPLY BRIEF IN SUPPORT OF ITS MOTION TO  
DISMISS PURSUANT TO FEDERAL RULE OF CIVIL PROCEDURE 12(b)(6)**

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## I. INTRODUCTION

The Supreme Court’s test for patentability under 35 U.S.C. § 101 is a simple two-step inquiry: (1) Are the claims directed to a patent-ineligible concept (such as a natural phenomenon)?; (2) If so, do additional non-routine elements transform the claim into a patent-eligible application of the otherwise ineligible concept? *Alice Corp. Pty. Ltd. v. CLS Bank Int’l*, 573 U.S. 208 (2014). If the final answer is no, then the claims are not patent-eligible. *Id.*

Here, it is undisputed that the circulating cell-free nucleic acids recited in the asserted claims are a natural phenomenon. And the patents repeatedly state that the additional recited techniques for detecting them—genotyping, high-throughput sequencing, and digital PCR—were not only known, but previously used to detect circulating cell-free nucleic acids that correlate with conditions such as cancer or fetal abnormalities. Plaintiffs argue in their Opposition that using these same known techniques to detect circulating cell-free nucleic acids corresponding to a *different* condition—here organ transplant rejection—makes the claims patentable. But using conventional methods known to be effective in detecting some natural phenomena (tumor or fetal cell-free nucleic acids) to detect a different natural phenomenon (donor-specific cell-free nucleic acids in an organ transplant recipient) is not patentable.

Natera’s Opening Brief demonstrates that the asserted claims are unpatentable using the only evidence that matters at the Rule 12(b)(6) stage: the words and history of the patents and the pleadings. By contrast, Plaintiffs’ Opposition relies on nearly 300 pages of extraneous and irrelevant “evidence” and numerous incorrect legal standards to manufacture unnecessary complexity for a straightforward inquiry. For example, Plaintiffs rely on an expert declaration that is procedurally improper, contradicts the words of the asserted patents, and uses conclusions to create the impression of a “fact intensive” and technologically “dense” inquiry unsuitable for early disposition. But Plaintiffs’ factually and legally erroneous arguments cannot change the answer to the Section 101

inquiry: Plaintiffs’ asserted claims apply conventional techniques to detect the natural phenomena of donor-specific cell-free nucleic acids that arise as a direct consequence of, and correlate to, a patient’s body rejecting a transplanted organ.

As discussed below, the Federal Circuit repeatedly has affirmed Section 101 dismissals under Rule 12, including for analogous claims more technically sophisticated than those here. This Court in fact recently held patents invalid at the Rule 12 stage, and should do so here. *In-Depth Test, LLC v. Maxim Integrated, Prods., Inc.*, 2018 WL 6617142, \*3-4 (D. Del. Dec. 18, 2018).

## **II. PLAINTIFFS’ EXTRANEOUS EVIDENCE SHOULD BE DISREGARDED**

To support their arguments, Plaintiffs rely almost entirely on two irrelevant sources that are not part of the pleadings: (1) a declaration (with exhibits) by Dr. Henry Furneaux, which contradicts the asserted patents; and (2) a misreading of Natera’s (not Plaintiffs’) patent filings and website. The Third Circuit has made clear that “a district court ruling on a motion to dismiss may not consider matters extraneous to the pleadings.” *In re Burlington Coat Factory Sec. Litig.*, 114 F.3d 1410, 1426 (3d Cir. 1997). Indeed, courts routinely reject expert testimony submitted to oppose a Rule 12 motion, including Section 101 motions. *Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 915 F.3d 743, 755 (Fed. Cir. 2019); *Ass’n of Irrigated Residents v. Fred Schakel Dairy*, 2008 WL 850136, at \*4 n.4 (E.D. Cal. Mar. 28, 2008). Courts also regularly disregard extraneous patents and advertising materials, like those relied on by Plaintiffs here, in deciding § 101 motions to dismiss. *Opp.* at 4, 12-13, 15; *O2 Media, LLC v. Narrative Sci., Inc.*, 149 F. Supp. 3d 984, 995 (N.D. Ill. 2016). Here, too, the Court should disregard Plaintiffs’ references to these extraneous materials and any arguments based upon them.

## **III. PLAINTIFFS MISSTATE AND MISAPPLY THE APPLICABLE § 101 LAW**

Under the properly applied *Alice/Mayo* test, Plaintiffs cannot demonstrate that the asserted claims are directed to anything beyond conventional techniques to detect the correlation between

donor-specific cell-free nucleic acids in a transplant recipient's circulation and rejection of a transplanted organ. Plaintiffs' Opposition does not even attempt to do so. Instead, Plaintiffs contend that their claims are patentable based on an erroneous application of the two-step *Alice/Mayo* inquiry that finds no support in the law and offer purportedly "factual" assertions that contradict the words of the patents themselves.<sup>1</sup> Plaintiffs' arguments should be rejected.

#### A. Plaintiffs Misapply *Alice/Mayo* Step One

*Alice/Mayo* Step One ("Step One") asks whether the asserted claims are directed to a natural phenomenon. *Alice*, 573 U.S. at 217. Here, the parties agree—and the patents themselves expressly recite—that donor-specific cell-free nucleic acids exist in the body of a transplant recipient. Br. at 10-11; Opp. at 5-6, 11; D.I. 11-1, Ex. B at 27:39-40 ('652 patent). The patents also expressly disclose that the amount of those nucleic acids correlates with transplant rejection. Br. at 10-11; D.I. 11-1, Ex. B at 27:61-67 ('652 patent). These nucleic acids indisputably exist irrespective of how or whether they are detected. But Plaintiffs ignore the patents' own descriptions of these natural phenomena, and instead base their Step One analysis on (1) the ***method of detecting*** of the cell-free nucleic acids, and (2) the ***transplant procedure*** prompting their existence. Opp. at 10-13. This is legally incorrect.

Plaintiffs' primary Step One argument is that the asserted claims are not directed to the natural phenomenon of donor-origin cell-free nucleic acids in transplant patients but rather to purportedly "novel processes for detecting" those nucleic acids. Opp. at 15. That is wrong. The Federal Circuit has made clear that the method of detection is immaterial to Step One as "laws of nature exist regardless of the methods used by humans to observe them." *Cleveland Clinic Found. v.*

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<sup>1</sup> Plaintiffs' Appendix A is improper attorney argument seeking to analogize the case law to the instant facts in excess of the 20-page limit for an opposition brief pursuant to Local Rule 7.1.3(a)(4). The Court should reject Plaintiffs' further attempt to use Appendix A to argue that claim length is a proxy for patent eligibility, as it is the *Alice/Mayo* test—not the length of the claims—that controls.

*True Health Diagnostics LLC*, 760 F. App'x 1013, 1019 (Fed. Cir. 2019).

The facts here are analogous to *Cleveland Clinic*, where the patents claimed detecting concentrations of the blood-borne protein Myeloperoxidase (“MPO”), which increase in patients with cardiovascular disease. *Id.* at 1015-17. The *Cleveland Clinic* claims recited techniques to identify blood-borne MPO, such as immunoassays and spectrophotometry, which are as complex (if not more) than the methods claimed here. *Id.* at 1016-17; Br. at 2-4. In holding the *Cleveland Clinic* claims ineligible, the Federal Circuit viewed the recitation of complex but well-known detection methods (immunoassays and spectrophotometry) as mere “draftsman’s art,” recognizing the claims were improperly directed to natural correlations between MPO and heart disease that exist “regardless of the methods used by humans to observe them.” *Id.* at 1018-19.

The same is true here. Donor-specific cell-free nucleic acids in a transplant recipient exist in the recipient’s blood and correlate with transplant rejection. Br. at 4-5. These nucleic acids result from biological processes in the transplant recipient’s body, and the recited detection methods—genotyping, high-throughput sequencing or digital PCR—do not create them. Rather, they exist irrespective of the detection methodology. *Id.* at 10-11. Plaintiffs’ attempt to shift the inquiry to alleged “human-developed techniques of the inventions” thus misses the mark. Opp. at 10-13.

Plaintiffs also argue—again in direct contradiction to the language of the asserted claims—that the patents “are not directed to nucleic acids, any general correlation with disease, or anything else that could be characterized as a natural phenomenon.” *Id.* at 11. But the claims themselves establish why this argument is incorrect. For example, Claim 1 of the ’497 patent recites “[a] method of detecting donor-specific circulating cell-free nucleic acids in a solid organ transplant recipient[.]” D.I. 11-1, Ex. A at 28:2-3. Claim 1 of the ’652 patent recites “[a] method for detecting transplant rejection, graft dysfunction, or organ failure,” D.I. 11-1, Ex. B at 27:39-40, by “determining a



quantity of the donor cell-free nucleic acids,” *id.* at 27:61-62, “wherein an increase in the quantity of the donor cell-free nucleic acids over time is indicative of transplant rejection, graft dysfunction, or organ failure.” *Id.* at 27:64-67. Claims like these that involve “detecting a natural law ‘with no meaningful non-routine steps’” are not patent eligible. *Athena Diagnostics*, 915 F.3d at 752 (quoting *Cleveland Clinic Found. v. True Health Diagnostics, LLC*, 859 F.3d 1352, 1361 (Fed. Cir. 2017)); *Br.* at 10-11; *infra* § III(B) (showing recited steps are routine).

Plaintiffs further contend that Step One is not satisfied because the claimed methods “are intended to be applied in the most unnatural circumstances—introduction of a foreign organ into a human body.” *Opp.* at 11-12. But Plaintiffs’ contention that a transplant is unnatural is irrelevant to Supreme Court precedent establishing that the body’s response to a foreign agent is still a natural phenomenon even if the agent is man-made. In *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, the Supreme Court invalidated claims reciting the body’s response to **man-made** thiopurine drugs. 566 U.S. 66, 72 (2012). The *Mayo* Court noted that some patients receiving thiopurine reacted by generating thiopurine metabolites measurable in their blood. *Id.* at 73-74, 77. The Court held that claims directed to measuring those blood-borne metabolites were unpatentable because the body’s reaction to thiopurine and the metabolite products thereof were natural phenomena. *Id.* at 77-80. The same is true here. A patient’s reaction to a foreign organ—including immune reactions resulting in increased donor-specific cell free nucleic acids—is a natural phenomenon.

Plaintiffs finally argue that the recited creation of “SNP profiles” makes the claims “more specific,” and thus not directed to natural phenomena. *Opp.* at 11. Not so. The claimed “profiles” describe yet another natural phenomenon—nothing more than a selected assortment of naturally occurring genetic variations detected in the sample. Indeed, the patents disclose that “any donor and recipient will vary at roughly three million SNP positions if fully genotyped.” D.I. 11-1, Ex. B at

13:42-44 ('652 patent); *id.* at 16:3-7; Br. at 15. The profiles select a number of SNPs where variation between the donor and recipient exists. D.I. 11-1, Ex. B at 13:44-66 ('652 patent). It is well-settled that such compilations of naturally-occurring genetic variations are unpatentable. *Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1375-76 (Fed. Cir. 2016) (finding claims directed to analyzing subsets of variations in genetic information unpatentable); *PerkinElmer, Inc. v. Intema Ltd.* 496 F. App'x 65, 66-68, 70-71 (Fed. Cir. 2012) (finding method of measuring levels of a profile of biomarkers from pregnancy to determine risk of Down's syndrome unpatentable).<sup>2</sup>

### **B. Plaintiffs Misapply *Alice/Mayo* Step Two**

In *Alice/Mayo* step two ("Step Two"), courts look for an inventive concept in order to "provide practical assurance that the process is more than a drafting effort designed to monopolize the [natural phenomenon] itself." *Mayo*, 556 U.S. at 77.<sup>3</sup> Courts look for something beyond "routine activity" to transform a natural phenomenon to patent-eligible subject matter. *Ulramercial, Inc. v. Hulu, LLC*, 772 F.3d 709, 714 (Fed. Cir. 2014). And the Federal Circuit has made clear that there is no "inventive concept" if claims "merely recite the use of ... existing ... technology" in connection with a natural phenomenon. *Content Extraction & Transmission LLC v. Wells Fargo Bank*, 776 F.3d 1343, 1348 (Fed. Cir. 2014); *Athena Diagnostics*, 915 F.3d at 748.

Beyond natural phenomena, the asserted claims recite nothing more than conventional

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<sup>2</sup> See also *Esoterix Genetic Labs. LLC v. Qiagen Inc.*, 133 F. Supp. 3d 349, 359-60 (D. Mass. 2015) (claims directed to correlation of certain nucleotide variances to drug responsiveness); *Genetic Techs. Ltd. v. Lab. Corp. of Am. Holdings*, 2014 WL 4379587, at \*10 (D. Del. Sept. 3, 2014) (method of analyzing sample to detect the presence of certain genetic variations).

<sup>3</sup> Plaintiffs' effort to replace the Section 101 *Alice/Mayo* inquiry with the obviousness standard under 35 U.S.C. § 103 is contrary to law. Plaintiffs assert that "prior art failures," "long-felt but unmet need," "skepticism of others in the field," and no "reasonable expectation of success" render the asserted claims patentable under Section 101. Opp. at 18-19. But these are issues properly examined when considering obviousness under § 103, not patentability under § 101. *In re Bilski*, 545 F.3d 943, 958 (Fed. Cir. 2008) (reversed on other grounds); *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406-07 (2007); *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097-98 (Fed. Cir. 1986).

techniques, such as genotyping, high throughput sequencing, and digital PCR. The patent describes *all of this* as “known in the art” to detect conditions such as cancer and fetal conditions. Br. at 12-15; D.I. 111-1, Ex. B at 6:57-7:36 (describing “genotyping,” “sequencing,” and “presence of sequences differing from a patient’s normal genotype ... to detect disease” as “known in the art”).

Plaintiffs’ Opposition focuses on the high throughput sequencing and digital PCR limitations of the asserted claims, explicitly conceding that “high-throughput analysis was known in the art.” Opp. at 16. But the thrust of Plaintiffs’ Step Two argument is that using these techniques *to detect donor-specific nucleic acids* makes them unconventional. *Id.* The Federal Circuit rejected the same reasoning under analogous circumstances in *Athena Diagnostics*, holding that use of known, conventional techniques to observe a natural phenomenon—like the claimed techniques here—is not patentable. 915 F.3d at 749. In *Athena Diagnostics*, the Federal Circuit affirmed a Rule 12(b)(6) order invalidating claims directed to detecting MuSK, a blood-borne antibody appearing in patients with a condition called Myasthenia Gravis. *Id.* at 748, 757. Recognizing the natural correlation between blood-borne MuSK antibodies and disease, the Federal Circuit rejected the plaintiff’s arguments that sophisticated but *conventional* techniques recited in the claims were sufficient to render the claims patentable. *Id.* at 753-55. *Athena Diagnostics* found that “the claims before us only involve detecting a natural law with no meaningful non-routine steps.” *Id.* at 752.

The same is true here. Donor-specific cell-free nucleic acids and their correlation with transplant rejection are a natural phenomenon, and the patents disclose digital PCR and high-throughput sequencing were known and used in the art to detect other natural phenomena, namely circulating or cell-free nucleic acids in oncology or prenatal screening. D.I. 11-1, Ex. B at 6:57-7:36 (’652 patent). As in *Athena Diagnostics*, using those conventional techniques to detect cell-free nucleic acids in an organ transplant context does not give rise to patent eligible subject matter.

Plaintiffs also use Dr. Furneaux’s declaration in an effort to manufacture a “question of fact” as to how digital PCR was used in the prior art. Opp. at 17. But Dr. Furneaux’s opinions are both procedurally improper and in direct conflict with the words of the patents—which explain that digital PCR was the tool of choice for detecting cell-free nucleic acids, even in *transplant cases* as early as 2006. D.I. 11-1, Ex. B at 8:1-8 (’652 patent); Opp. at 16-17; Br. at 12-13.

Plaintiffs also contend that the asserted claims are patentable because the “ordered combination” of the methods makes “the claimed invention as a whole” unconventional. Opp. at 17-18. Plaintiffs again rely entirely on Dr. Furneaux’s opinion to support their argument. And, again, Dr. Furneaux’s conclusory statements contradict the patents’ language. Neither the Plaintiffs nor Dr. Furneaux identify *any statements in the patents* that say the “ordered combination” of these routine techniques is unconventional. *Id.* To the contrary, the patents describe well-established use of the precise combination of these techniques, including “genotyping,” “shotgun sequencing,” and others to do “quantitative assay[s]” for “detecting” cancer, fetal disorders, and other conditions, wherein “[i]n all these applications of circulating nucleic acids, the presence of sequences differing from a patient’s normal genotype has been used to detect disease.” D.I. 11-1, Ex. B at 6:57-7:36 (’652 patent). Applying these established combinations to detect another natural phenomenon (circulating nucleic acids in an organ transplant recipient) does not make those combinations unconventional.

Like Step One, Plaintiffs fail at Step Two to rebut Natera’s showing—based on the words of the patents themselves—that the asserted claims are directed to nothing more than using techniques known in the art for detecting natural phenomena. This should end the inquiry.

#### IV. PLAINTIFFS’ PRAISE OF THE INVENTORS’ WORK IS IMMATERIAL

Plaintiffs’ Opposition attempts to paint the named inventors as “pioneer[ing],” presumably to imply that their claimed inventions must be patentable and a finding otherwise would be unjust. Opp. at 1, 7. But even if Plaintiffs’ characterizations of the inventor’s work were deemed true, neither the

amount of research done nor its scientific significance informs the question of patentability. In fact, the Federal Circuit has held that even the most “[g]roundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry.” *Genetic Techs.*, 818 F.3d at 1374 (internal quotations and citation omitted). Rather, it is the *Alice/Mayo* inquiry (which the claims here fail), and not the alleged “genius” of the inventors, that controls.

## V. PLAINTIFFS’ PREEMPTION AND CLAIMED ADVANCE ARGUMENTS FAIL

Plaintiffs contend that Natera does not show complete “preemption,” which according to Plaintiffs is key to the Section 101 analysis. Opp. at 15. Not so. While “preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility.” *FairWarning IP, LLC v. Iatric Sys., Inc.*, 839 F.3d 1089, 1098 (Fed. Cir. 2016). “Where a patent’s claims are deemed only to disclose patent ineligible subject matter under the *Mayo* framework, as they are in this case, preemption concerns are fully addressed and made moot.” *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1379 (Fed. Cir. 2015); *Money Suite Co. v. 21<sup>st</sup> Century Ins. & Fin. Servs., Inc.*, 2015 WL 436160, at \*5 (D. Del. Jan. 27, 2015).

Plaintiffs also argue that Natera did not evaluate the patents’ “claimed advance” over the prior art. Opp. at 14. But the only “advance” over the prior art described in the patents is the use of known methods to detect naturally occurring donor-specific cell-free nucleic acids in transplant recipients. As the patents consistently explain, these same known methods were previously used to detect naturally occurring circulating DNA in, for example, pregnant women or cancer patients. *E.g.*, D.I. 11-1, Ex. B at 6:57-7:36 (’652 patent); Br. at 18-19. Where, like here, the “claimed advance” over the prior art is simply a new natural phenomenon observed using conventional methods, the claimed invention is not patentable. *Cleveland Clinic*, 859 F.3d at 1360-61; *XY, LLC v. Trans Ova Genetics, LC*, 333 F. Supp. 3d 1097, 1105 (D. Colo. 2018); *Nat. Alts. Int’l, Inc. v. Creative Compounds, LLC*, 2017 U.S. Dist. LEXIS 143434, at \*32 (S.D. Cal. Sep. 5, 2017).

Plaintiffs’ attempt to rely on *Rapid Litig. Mgmt. Ltd v. CellzDirect, Inc.*, 827 F.3d 1042, 1050 (Fed. Cir. 2016) to salvage their claims also fails, as that case is readily distinguishable and was distinguished based on analogous facts by the Court in *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 356 F. Supp. 3d 925, 933-35 (N.D. Cal. 2018). Opp. at 13-14. The claimed method in *CellzDirect* resulted in a type of **unnatural** composition—a “desired preparation of multi-cryopreserved hepatocytes”—based on an unconventional freeze-thaw cycle method. 827 F.3d at 1048-49. Creating a population of cells resilient to an unnatural laboratory process occurring at very low temperatures is not comparable to detecting naturally occurring donor-specific cell-free nucleic acids. And unlike the claims in *CellzDirect*, these claims do not make anything new from donor-specific cell-free nucleic acids, and use conventional methods to detect them.

#### **VI. PLAINTIFFS’ “CLAIM CONSTRUCTION” ARGUMENTS REGARDING THE ’652 PATENT ARE A RED HERRING**

Natera demonstrated that Plaintiffs have not, and cannot, plead infringement of the elements of the ’652 patent claims. Br. at 19-20. Contrary to Plaintiffs’ Opposition, claim construction is not required to resolve this issue as the meanings of the terms are plainly discernable from the intrinsic record. *Id.*; Opp. at 19-20; *United States Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997). But even if the Court were to construe the claims, the record demonstrates that under any construction—which is an issue of law resolvable here—Natera is not infringing the ’652 patent claims. *Id.*

#### **VII. CONCLUSION**

For the reasons stated above and in its Opening Brief, Natera requests that the Court dismiss the Complaint in its entirety with prejudice.

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**CERTIFICATE OF SERVICE**

I hereby certify that on June 24, 2019, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on June 24, 2019, upon the following in the manner indicated:

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# **EXHIBIT 4**

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

CAREDX, INC. and THE BOARD OF	)	
TRUSTEES OF THE LELAND STANFORD	)	
JUNIOR UNIVERSITY,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	C.A. No. 19-567 (CFC) (CJB)
	)	CONSOLIDATED
NATERA, INC.,	)	
	)	
Defendant.	)	

**NATERA, INC.'S OBJECTIONS TO MAGISTRATE JUDGE'S REPORT AND  
RECOMMENDATION ON ITS MOTION TO DISMISS**

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## I. PRELIMINARY STATEMENT

Natera, Inc. (“Natera”) objects to the recommendation (D.I. 53, or “R&R”) to deny Natera’s Motion to Dismiss (D.I. 10, 19, or “Motion”). Natera’s Motion shows that the Asserted Claims<sup>1</sup> seek to cover the patent-ineligible natural phenomena of donor-derived cell-free DNA (“cfDNA”) in an organ transplant recipient’s body, and its correlation to transplant health. The claimed methods use only conventional techniques to do this.<sup>2</sup> Hence, the Asserted patents claim natural phenomena unpatentable under the Supreme Court’s governing framework in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66 (2012) and *Alice Corp. Pty. Ltd. v. CLS Bank Int’l*, 573 U.S. 208 (2014).

The R&R erroneously recommended that the Court find the Asserted Claims to be “directed to” patent eligible subject matter. Specifically, the R&R stated that the Asserted Claims are “directed to” a “*purportedly* new, unconventional combination of steps” rather than the recited “natural law itself.” *Id.* ¶ 8.<sup>3</sup> But the R&R did not base this recommendation upon an evidence-based analysis of whether the recited methods for detection are actually conventional, as required by *Mayo*, *Alice*, and controlling Federal Circuit law. Rather, the R&R assumed that they must be unconventional because the patents’ written description states that the natural phenomena to be detected were already known and that others in the field allegedly faced problems in attempting to detect them. In reaching this conclusion, the R&R disregarded substantial evidence in the patents admitting that all of the steps recited in the actual claim

<sup>1</sup> These are the representative claims (Claim 1) of U.S. Patent Nos. 8,703,652 (the “‘652 Patent”), D.I. 11-1 (Ex. B) and 9,845,497 (the “‘497 Patent”), *id.* (Ex. A).

<sup>2</sup> For background of the claims and technology, see D.I. 10 at 2-5; 11/21/19 Hr’g Tr. at 6-14; 11/21/19 Natera Hr’g Presentation, Slides 3-13.

<sup>3</sup> Emphasis is added herein unless otherwise noted.

language, in the claimed combinations, were routine and conventional. That was error, leading to a recommendation that contradicts well-settled law in which “detection” claims like these are consistently invalidated for being “directed to” natural phenomena.

Because the R&R’s recommendation is contrary to substantial, highly relevant record evidence and established legal authority, Natera requests that the Court reject the R&R and find the Asserted Claims unpatentable under Section 101 upon its review *de novo*. 28 U.S.C. § 636(b)(1)(C); Fed. R. Civ. P. 72(b).

## II. ARGUMENT

### A. The R&R Erred In Assuming That The Claimed Steps Are Unconventional Rather Than Making The Required Legal Determination That They Are

The R&R recommended a finding that “the claims appear to be ‘directed to’ [] *particular methods for detecting*—and not to the *fact or existence of the natural phenomenon* itself.” R&R n.8 (italics in original). When the R&R determined that the claims were directed to the recited methods rather than a natural phenomenon, it was required to address whether those methods were routine and conventional.<sup>4</sup> Because the R&R did not do this, it committed legal error. *See id.* n.8.

It is well settled that method claims that “involve detecting a natural law” are (unpatentably) “directed to” that natural law if they recite only “standard techniques for observing” it. *Athena Diagnostics, Inc. v. Mayo Collaborative Servs.*, 915 F.3d 743, 752 (Fed. Cir. 2019) (quoting *Cleveland Clinic Found. v. True Health Diagnostics, LLC*, 859 F.3d 1352, 1361 (Fed. Cir. 2017)). Indeed, “claims that merely recite observing naturally occurring

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<sup>4</sup> The cited authorities variously address conventionality at Step One or Step Two of the *Alice* framework. Here, the R&R did not address conventionality at all, so there is error irrespective of the stage in which it occurred.

biological correlations ‘with no meaningful non-routine steps in between’ are directed to a natural law.” *Id.* at 751 (quoting *Cleveland Clinic*, 859 F.3d at 1361).

Here, there is no dispute that the claims recite a method for “detecting [the] natural law” of donor-derived cfDNA in the body of a transplant recipient, and then correlating it to transplant rejection (another natural law).<sup>5,6</sup> *See id.* at 752; R&R ¶ 3 (recognizing cfDNA in transplant recipient’s body and its correlation to rejection are naturally occurring). This satisfies the first part of the section 101 inquiry. *Athena*, 915 F.3d at 752. But the R&R was legally required to answer the rest of the inquiry: whether the recited detection method is unconventional. The R&R did not do so. Indeed, it made “no conclusions as to who is right or who is wrong” on whether “the claims amount[] to the use of conventional methods well-known in the art to determine the presence of donor cfDNA in the body.” R&R n.8.

The required analysis would have factored in the numerous admissions by the patentee that every step in the claimed methods, as well as the combination of methods as claimed, were routine and well-known. These admissions are catalogued in Natera’s briefing, summarized below, and compel a finding of patent ineligibility. *See, e.g.*, Motion at 12-17; D.I. 11-1 (Ex. C). For example:

- ’652 Patent Claim 1(a) and ’497 Patent Claim 1(c) recite obtaining a biological “sample.” *See* ’652 Patent at 6:57-67; 10:11-12, explaining this was well-known and conventional.

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<sup>5</sup> *See* D.I. 11-1 (Ex. B (’652 Patent)) at 27:39-40 (reciting “[a] method for detecting transplant rejection, graft dysfunction, or organ failure...”); D.I. 11-1 (Ex. A (’497 Patent)) at 28:2-3 (reciting “[a] method of detecting donor-specific circulating cell-free nucleic acids in a solid organ transplant recipient.”).

<sup>6</sup> This is consistent with the patentee’s own admissions to the patent office. Ex. A [Nov. 14, 2016 Response (Cited in support of an argument raised below).] (“As currently amended the claims are directed to a method of detecting donor-specific cell-free nucleic acids [e.g., cfDNA] in a solid organ transplant recipient...”)

- '652 Patent Claim 1(b) and '497 Patent Claims 1 (a) and (b) recite “genotyping.” See '652 Patent at 13:52-67; 20:31-51, explaining this was well-known and conventional.
- '652 Patent Claim 1(b) and '497 Patent Claims 1(a) and (b) recite establishing “polymorphism profile” or “single nucleotide polymorphism (SNP) profile” for detecting donor cell-free nucleic acids. See '652 Patent at 11:24-26; 11:33-34; 13:51-67; 20:31-51, explaining this was well-known and conventional.
- '652 Patent Claim 1(c) and '497 Patent Claim 1(d) recite “multiplex sequencing” or “high-throughput sequencing or digital polymerase chain reaction (dPCR).” See '652 Patent at 7:23-28; 9:8-14; 14:58-67; 15:2-8; 15:22-17:14, 21:5-8, explaining this was well-known and conventional.
- '652 Patent Claim 1(d) recites correlating the amount of cell-free nucleic acid to transplant status with a certain sensitivity of the method; '497 Patent Claim 1(d) recites determining the amount of circulating donor cell-free nucleic acid with a certain sensitivity of the method. See '652 Patent at 9:8-14; 17:1-15, 17:22-25; 21:5-8; 21:31-44, explaining this was well-known and conventional.
- See *Id.* at 6:57-7:46; 7:30-36, describing the claimed combination as well-known for analyzing cfDNA in other contexts: “In all these applications of circulating nucleic acids, the presence of sequences differing from a patient’s normal genotype has been used to detect disease. In cancer, mutations of genes are a tell-tale sign of the advance of the disease; in fetal diagnostics, the detection of sequences specific to the fetus compared to maternal DNA allows for analysis of the health of the fetus.”

**B. The R&R Misinterpreted The Written Description To Assume That The Claimed Methods Are Unconventional**

The R&R erroneously assumed—without addressing the overwhelmingly contrary admissions in the patents themselves—that it is a “*purportedly* new, unconventional combination of steps that the claims are directed to, not the natural law itself.” R&R fn. 8. Making this assumption, the R&R also erroneously relied on the background invention story told in the written description to extrapolate a conclusion that the claims must be patent eligible.

For example, the R&R highlighted background in the written description stating that others in the field had “for years been attempting to find ways to test for and detect the presence of such donor-specific cfDNA.” *Id.* ¶ 6. But the Federal Circuit has rejected such attempts to read aspirational statements about problem solving into patent claims for the purpose of



ascertaining their eligibility. See *BSG Tech LLC v. Buyseasons, Inc.*, 899 F.3d 1281, 1283-84 (Fed. Cir. 2018); *Intellectual Ventures I LLC v. Erie Indemnity Co.*, 850 F.3d 1315, 1325-26 (Fed. Cir. 2017); *In re TLI Commc'ns LLC Patent Litig.*, 823 F.3d 607, 609-10 (Fed. Cir. 2016).

The R&R also erred in assuming that the claims cannot be directed to the recited natural phenomenon because the written description states it was already well-known. The R&R rhetorically asked: “How could it be the case that the ... ‘focus’ of the purportedly representative claims of the patents is to a naturally-occurring correlation, when the patentee repeatedly states that this very correlation was already well-known in the art?” R&R ¶ 7. But the Asserted Claims do not become patent-eligible simply because the patentee admits that it did not discover the natural law it seeks to claim. And the Supreme Court has answered the question posed by the R&R, holding that claims directed to a natural law are patent ineligible irrespective of whether the natural law is old or new. Indeed, the Supreme Court in *Mayo* found the claims at issue patent-ineligible even though “scientists already understood” the natural law (correlation of blood metabolites to disease) before the patent. *Mayo*, 566 U.S. at 73-74; see also *23andMe, Inc. v. Ancestry.com DNA, LLC*, 356 F. Supp. 3d 889, 904-05 (N.D. Cal. 2018), *aff'd*, 778 F. App'x 966 (Fed. Cir. 2019).

“[W]hile the specification may help illuminate the true focus of a claim, when analyzing patent eligibility, reliance on the specification must always yield to the claim language in identifying that focus.” *ChargePoint, Inc. v. SemaConnect, Inc.*, 920 F.3d 759, 766-69 (Fed. Cir. 2019). Here, the claim language is “directed to” unpatentable subject matter: testing a sample (transplant patient’s blood), detecting a natural phenomenon (donor-derived cfDNA) in it, and correlating that to disease (transplant rejection). As discussed above, the methods use only routine method steps for detecting this naturally-occurring cfDNA and “correlating” it to disease,

which is not patent eligible. That the R&R did not account for the conventionality of the methods against the evidence provided is error, and leads to a result that contradicts binding precedent.

**C. The R&R Contradicts Settled Precedent Holding Routine And Conventional Detection Methods Unpatentable**

In every case in which the Supreme Court and Federal Circuit have been presented with claims analogous to the Asserted Claims, they have been held to be “directed to” patent ineligible subject matter. *See Athena*, 915 F.3d at 752-53; *Cleveland Clinic*, 859 F.3d at 1360-61; *Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1376 (Fed. Cir. 2016); *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1373-77 (Fed. Cir. 2015). The R&R’s misapplication of the *Mayo/Alice* framework runs afoul of this controlling precedent.

For example, in *Ariosa* the Federal Circuit addressed claims to methods that are analogous to those here—methods directed to detecting naturally occurring fetal cfDNA in a pregnant woman’s blood—and found they were directed to a natural phenomenon because the claimed “method steps were well-understood, conventional and routine.” 788 F.3d at 1376-77. Similarly, in *Athena*,<sup>7</sup> the Federal Circuit found methods for detecting naturally occurring auto-antibodies “directed to” a natural law, emphasizing that, like here, the patent stated the claims “may be performed in accordance with [] assay techniques known per se in the art,” and described those recited in the claims as “standard techniques in the art.” 915 F.3d at 748. The *Athena* panel concluded that “[c]laiming a natural cause of an ailment and well-known means of observing it is not eligible for patent because such a claim in effect only encompasses the natural law itself.” *Id.* at 752-53.

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<sup>7</sup> The *Athena* claims recited a method involving “contacting MuSK or [related chemical entities] having a suitable label thereon ... immunoprecipitating any antibody/MuSk complex [or related complexes] ... and monitoring for said label on any of said antibody/Musk complex [or related complex] ...” 915 F.3d at 747.

Likewise, in *Cleveland Clinic*, the Federal Circuit found that similar diagnostic claims were “directed to” a natural phenomenon, emphasizing that, like here, “[t]he specifications of the testing patents confirm that known testing methods could be used to detect [the natural phenomenon], and that there were commercially available testing kits for [the natural phenomenon] detection.” 859 F.3d at 1361.<sup>8</sup> Similarly, in *Genetic Technologies*,<sup>9</sup> the Federal Circuit found the diagnostic claim “directed to” a natural law because it “does not purport to identify novel detection techniques.” 818 F.3d at 1374-76. And in *INO Therapeutics LLC v. Praxair Distrib. Inc.*, the Federal Circuit found “the [] patents do not claim an improved laboratory method.” 782 F. App’x 1001, 1006-09 (Fed. Cir. 2019).

In the face of all of this precedent,<sup>10</sup> the R&R cites a single case, *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1045-50 (Fed. Cir. 2016), in support of its recommendation. R&R ¶ 9. But that reliance is misplaced. In *CellzDirect*, the court found the claims at issue directed not to the natural phenomenon of a liver cell’s ability to survive multiple freeze-thaw cycles, but rather “to a new and useful laboratory technique for preserving [liver cells],” and “producing a desired preparation” therefrom—a preparation that that did not occur in nature. *Id.* at 1046, 1048. The Court then discussed (hypothetically) how the technique itself would be unconventional because it applied multiple freeze-thaw cycles to the cells—an approach contrary to the prior art teachings. *Id.* at 1051. That case is, thus, distinguishable from the case at bar, and from the precedent discussed above, because here (as in *Athena*, *Cleveland Clinic*, and the other

<sup>8</sup> The *Cleveland Clinic* claims recited methods for administering drugs based on “elevated levels of [MPO] mass and/or activity,” which correlates to disease, comprising “performing an enzyme linked immunosorbent assay (ELISA)” and other complicated laboratory techniques for detecting MPO. 859 F.3d at 1357-58.

<sup>9</sup> The *Genetic Technologies* patents claimed “a method for detection” of certain genetic sequences comprising “amplifying genomic DNA” with a “primer pair” having a number of technical characteristics. 818 F.3d at 1372.

<sup>10</sup> The R&R references *Athena* in a single *Cf.* citation at n.10.

Federal Circuit cases) the claims use only conventional techniques to detect donor-derived cfDNA *as it exists in nature*. See *Cleveland Clinic*, 859 F.3d at 1361 (distinguishing *CellzDirect*); *Athena*, 915 F.3d at 751-52 (same); see also *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 356 F. Supp. 3d 925, 933 (N.D. Cal. 2018) (same).

### III. CONCLUSION

The R&R's reasoning contradicts well-settled law by deeming any method—even one that detects a natural phenomenon using conventional techniques—to be patent eligible as long as the patentee *purports* that the method is unconventional. This reasoning is contradictory to *Mayo*, *Alice*, *Athena*, *Cleveland Clinic*, *Genetic Technologies*, *Ariosa*, and *INO Therapeutics*. This Court must determine whether the claimed methods for detecting a natural phenomenon are unconventional. In so doing, it cannot make assumptions or elevate aspirational statements in the written descriptions over the patentee's admissions that the claimed detection steps are entirely conventional. The R&R should be rejected, and Natera's Motion to dismiss should be granted.

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February 24, 2020

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**CERTIFICATE OF COMPLIANCE**

I hereby certify that this brief has been prepared in Times New Roman 12-point typeface using Microsoft Word, and contains 2,499 words as determined by the Word Count feature of Microsoft Word.

February 24, 2020

/s/Derek J. Fahnestock

**CERTIFICATION PURSUANT TO DISTRICT OF DELAWARE STANDING ORDER  
FOR OBJECTIONS FILED UNDER FED. R. CIV. P. 72**

Pursuant to paragraph 5 of the Court's Standing Order for Objections Filed Under Fed. R. Civ. P. 72, Defendant Natera, Inc. hereby certifies that the foregoing objections do not raise any legal or factual arguments that were not previously raised before Magistrate Judge Burke.

February 24, 2020

/s/ Derek J. Fahnestock

**CERTIFICATE OF SERVICE**

I hereby certify that on February 24, 2020, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on February 24, 2020, upon the following in the manner indicated:

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# EXHIBIT A

Electronically Filed

<p style="text-align: center;"><b>AMENDMENT UNDER 37 C.F.R. §1.11</b></p> <p>Address to: Mail Stop Amendment Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450</p>	Attorney Docket No.	STAN-706CON
	Confirmation No.	5088
	First Named Inventor	Quake, Stephen R.
	Application Number	14/188,455
	Filing Date	February 24, 2014
	Group Art Unit	1639
	Examiner Name	BUNKER, AMY M
	Title:	<i>“Non-Invasive Diagnosis of Graft Rejection in Organ Transplant Patients”</i>

Sir:

This amendment is responsive to the Office Action dated August 11, 2016 for which a three-month period for response was given making this response due on or before November 11, 2016. In view of the amendments to the claims and the remarks put forth below, reconsideration and allowance are respectfully requested.

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Listing of the Claims:

- 1 - 35. (Cancelled)
36. (Currently amended ) A method of detecting donor-specific cell-free nucleic acids in a solid organ transplant recipient, the method comprising:
- (a) providing a biological sample from a subject who has received [[a]] the solid organ transplant from a donor, wherein the biological sample comprises cell-free nucleic acids from the transplant; and
  - (b) determining an amount of donor specific cell-free nucleic acids from the solid organ transplant in the biological sample wherein determining the amount comprises detecting a homozygous or heterozygous polymorphism within the donor specific cell-free nucleic acids from the solid organ transplant by conducting at least one of the following assay~~[[s:]]~~, wherein the at least one assay comprises high-throughput sequencing~~[[,]]~~ or digital polymerase chain reaction (dPCR).
37. (Withdrawn) The method of claim 118, wherein the threshold value is predetermined.
38. (Withdrawn) The method of claim 118, wherein the threshold value is a normative value for clinically stable post-transplantation patients with no evidence of transplant rejection or other pathologies.
39. (Cancelled)
40. (Withdrawn) The method of claim 118, wherein a change in transplant status or outcome is indicated when the amount of cell-free nucleic acids from the transplant is above the threshold value.
41. (Withdrawn) The method of claim 40, wherein the change in transplant status or outcome is transplant rejection.
42. (Withdrawn) The method of claim 41, wherein the transplant rejection is selected from the group consisting of acute rejection and chronic rejection.

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43. (Withdrawn) The method of claim 40, wherein the change in transplant status or outcome is non-rejection based transplant injury.
44. (Withdrawn) The method of claim 43, wherein the non-rejection based transplant injury is selected from the group consisting of ischemic injury, viral infection, perioperative ischemia, reperfusion injury, hypertension, physiological stress, injuries due to reactive oxygen species and injuries caused by pharmaceutical agents.
45. (Withdrawn) The method of claim 40, wherein the amount of cell-free nucleic acids from the transplant is below a second threshold value and is indicative of a transplant status or outcome less serious than rejection.
46. (Withdrawn) The method of claim 45, wherein the transplant status or outcome is viral infection.
47. (Withdrawn) The method of claim 118, wherein the threshold value is the amount of cell-free nucleic acids from the transplant present in a second biological sample obtained from the subject at a different point in time than the time at which the biological sample is obtained.
48. (Withdrawn) The method of claim 47, wherein the second biological sample is obtained from the subject prior to the biological sample and wherein an increase in the amount of cell-free nucleic acids from the transplant in the biological sample compared to the threshold value is indicative of transplant rejection.
49. (Withdrawn) The method of claim 118, wherein the amount of cell-free nucleic acids from the transplant is below or equal to the threshold value and is indicative of graft tolerance or graft survival.
50. (Withdrawn) The method of claim 118, wherein the amount of cell-free nucleic acids from the transplant temporarily increases to a level above the threshold value and then

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decreases to below or equal to the threshold value and indicates a transplant status or outcome less serious than rejection.

51. (Withdrawn) The method of claim 50, wherein the transplant status or outcome is viral infection.
52. (Withdrawn) The method of claim 119, wherein the transplant condition is selected from the group consisting of rejection, tolerance, non-rejection based transplant injury, transplant function, transplant survival, chronic transplant injury, and titer pharmacological immunosuppression.
53. (Previously presented) The method of claim 36, wherein the biological sample is selected from the group consisting of blood, sweat, tears, ear flow, sputum, lymph, bone marrow suspension, saliva, semen, vaginal flow, cerebrospinal fluid, brain fluid, ascites, breast milk, stool, secretions of the respiratory, intestinal or genitourinary tracts fluid, and a lavage of a tissue, organ, or tissue that has been removed from organs.
54. (Previously Presented) The method of claim 36, wherein the biological sample is blood.
55. (Currently Amended) The method of claim 36, wherein the solid organ transplant is selected from the group consisting of a kidney transplant, heart transplant, liver transplant, pancreas transplant, lung transplant, intestine transplant, skin transplant, and any combination thereof.
56. (Cancelled)
57. (Currently Amended) The method of claim 36, wherein the at least one assay is a high-throughput sequencing assay and the high-throughput sequencing assay generates at least 1,000 sequence reads per hour.
58. (Currently Amended) The method of claim 36, wherein the at least one assay is a high-throughput sequencing assay comprising a next-generation sequencing assay.

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59. (Previous Presented) The method of claim 58, wherein the high-throughput sequencing assay generates sequencing reads of at least 36 bases.
60. (Currently Amended) The method of claim 36, wherein the homozygous or heterozygous polymorphism is selected from the group consisting of a single nucleotide polymorphism (SNP), restriction fragment length polymorphism (RFLP), short tandem repeat (STR), variable number of tandem repeats (VNTRs), hypervariable region, minisatellite, dinucleotide repeat, trinucleotide repeat, tetranucleotide repeat, simple sequence repeat, and insertion element such as Alu.
61. (Currently Amended) The method of claim 36, wherein the homozygous or heterozygous polymorphism is a homozygous or heterozygous SNP.
62. (Currently Amended) The method of claim 61, wherein at least ten different homozygous or heterozygous SNPs are detected.
63. (Currently Amended) The method of claim ~~[[119]]~~ 36, further comprising a step of administering a therapeutic regimen to treat the ~~transplant condition~~ solid organ transplant recipient.
64. (Previously Presented) The method of claim 63, wherein the therapeutic regimen comprises administering an immunosuppressant treatment.
65. (Currently Amended) The method of claim ~~[[119]]~~ 63, further comprising a step of increasing or decreasing an immunosuppressive treatment as a result of ~~the detecting of the transplant condition~~ determining the amount of donor-specific cell-free nucleic acids from the solid organ transplant in the biological sample.
66. (Previously Presented) The method of claim 36, wherein the biological sample is a DNA sample.
67. (Previously Presented) The method of claim 36, wherein the subject is a human subject.



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68. (Previously Presented) The method of claim 36, wherein the method further comprises obtaining a polymorphism profile for the subject, the donor, or both the subject and the donor.
69. (Previously Presented) The method of claim 36, wherein the method further comprises obtaining a polymorphism profile for the subject.
70. (Previously Presented) The method of claim 69, wherein the method comprises using the obtained polymorphism profile in the detection of the cell-free nucleic acids from the transplant.
71. (Currently Amended) The method of claim 36, wherein the amount is the amount of donor specific cell-free nucleic acids from the transplant in the biological sample relative to [[the]] a total amount of nucleic acids in the biological sample.
72. (Currently Amended) The method of claim 36, wherein an amplification reaction is performed on the nucleic acids in the biological sample prior to determining the amount of donor specific cell-free nucleic acids from the transplant in the biological sample.
73. (Withdrawn) The method of claim 118, wherein the amount of cell-free nucleic acids from the transplant is above the threshold value and is indicative of graft dysfunction.
74. (Currently Amended) The method of claim ~~[[56]]~~57, wherein the high-throughput sequencing assay is a shotgun sequencing assay.
75. (Currently Amended) The method of claim 36, wherein the donor-specific cell-free nucleic acids from the transplant in the biological sample are DNA, RNA, mRNA, miRNA, double-stranded DNA, single-stranded DNA, single-stranded DNA hairpins, DNA/RNA hybrids, RNA hairpins, or a combination thereof.
76. (Previously Presented) The method of claim 36, wherein the cell-free nucleic acids from the transplant in the biological sample are RNA.

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77. (Previously Presented) The method of claim 76, wherein the cell-free nucleic acids from the transplant are organ-specific RNA transcripts.

78. (Previously Presented) The method of claim 36, further comprising genotyping the donor, the subject or both the donor and the subject prior to the determining in step (b).

79. (Previously Presented) The method of claim 36, further comprising genotyping the donor, the subject, or both the donor and the subject simultaneously with the determining in step (b).

80. (Previously Presented) The method of claims 78 or 79, wherein the genotyping comprises obtaining a single nucleotide polymorphism (SNP) profile for the donor, the subject, or both the donor and the subject.

81. (Previously Presented) The method of claims 78 or 79, wherein the genotyping comprises obtaining a SNP profile for the subject.

82. (Previously Presented) The method of claim 80, wherein the SNP profile comprises informative homozygous and heterozygous SNPs.

83. (Currently amended) The method of claim 82, wherein the method further comprises multiplying the number of informative heterozygous SNP molecules from the transplant by a factor of two.

84 - 87. (Cancelled)

88. (Currently Amended) The method of claim 36, wherein [[the]] sensitivity of the method is greater than 56%.

89. (Currently Amended) The method of claim 36, wherein the determining comprises detecting donor specific cell-free nucleic acids from the transplant wherein the donor specific cell-free nucleic acids from the transplant are at least 0.03% of [[the]] total cell-free nucleic acids in the sample.



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90. (Cancelled)

91. (Currently Amended) The method of claim 36, wherein the high-throughput sequencing assay method has a sequencing\_error rate of less than 1.5% for detecting cell-free nucleic acids from the transplant.

92. (Currently Amended) The method of claim 36, wherein the high-throughput sequencing assay method has resequencing error rate of less than 0.003% for detecting cell-free nucleic acids from the transplant.

93. (Withdrawn) A method of detecting a transplant condition, the method comprising:

(a) providing a biological sample from a subject who has received a transplant from a donor, wherein the biological sample comprises circulating nucleic acids from the donor;

(b) determining an amount of circulating nucleic acids from the donor in the biological sample wherein the determining comprises conducting a reaction to detect at least 20 different polymorphisms in the circulating nucleic acids from the donor; and

(c) using the amount of circulating nucleic acids from the donor to detect the transplant condition.

94. (Withdrawn) The method of claim 93, wherein the circulating nucleic acids from the donor are circulating cell-free nucleic acids.

95. (Withdrawn) The method of claim 93, wherein the circulating nucleic acids from the donor are nucleic acids from circulating donor cells.

96. (Withdrawn) The method of claim 93, wherein the reaction is a sequencing reaction, digital polymerase chain reaction (PCR) or array hybridization reaction.

97. (Withdrawn) The method of claim 93, wherein the biological sample is blood.
98. (Withdrawn) The method of claim 93, wherein the at least ten polymorphisms are selected from the group consisting of a single nucleotide polymorphism (SNP), restriction fragment length polymorphism (RFLP), short tandem repeat (STR), variable number of tandem repeats (VNTRs), hypervariable region, minisatellite, dinucleotide repeat, trinucleotide repeat, tetranucleotide repeat, simple sequence repeat, and insertion element such as Alu.
99. (Withdrawn) The method of claim 93, wherein the at least ten different polymorphisms comprise a SNP.
100. (Withdrawn) The method of claim 93, wherein the at least 20 different polymorphisms comprise at least 20 different SNPs.
101. (Withdrawn) The method of claim 93, wherein the at least 20 different polymorphisms are at least 50 different SNPs.
102. (Withdrawn) The method of claim 93, wherein the determining comprises determining which of the at least 20 polymorphisms are informative polymorphisms.
103. (Withdrawn) A method of detecting and treating a transplant condition, the method comprising:
- (a) providing a biological sample from a subject who has received a transplant from a donor, wherein the subject has received a therapeutic regimen and wherein the biological sample comprises cell-free nucleic acids from the donor;
  - (b) determining an amount of the cell-free nucleic acids from the donor in the biological sample, wherein the determining comprises conducting a sequencing reaction, digital polymerase chain reaction, or array hybridization reaction;
  - (c) using the amount of the cell-free nucleic acids to detect the transplant condition; and
  - (d) adjusting the therapeutic regimen for the subject based on the amount of the cell-free nucleic acids from the donor in the biological sample.

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104. (Withdrawn) The method of claim 103, wherein the therapeutic regimen is an immunosuppressant regimen.
105. (Withdrawn) The method of claim 103, wherein adjusting the therapeutic regimen comprises increasing the potency of the therapeutic regimen.
106. (Withdrawn) The method of claim 103, wherein adjusting the therapeutic regimen comprises decreasing the potency of the therapeutic regimen.
107. (Withdrawn) The method of claim 103, wherein the transplant condition is transplant rejection.
108. (Withdrawn) A method of detecting a transplant condition in a subject who has received a transplant from a donor comprising:
  - (a) providing a biological sample from the subject who has received a transplant from the donor, wherein the biological sample comprises circulating RNA from the donor;
  - (b) specifically determining an amount of circulating RNA from the donor in the biological sample wherein the determining the amount comprises detecting a sequence within the circulating RNA; and
  - (c) using the amount of circulating RNA from the donor to detect the transplant condition.
109. (Withdrawn) The method of claim 108, wherein the circulating RNA from the donor is circulating cell-free RNA.
110. (Withdrawn) The method of claim 108, wherein the circulating RNA from the donor is circulating organ-specific RNA.
111. (Withdrawn) A method of detecting a transplant condition, the method comprising:
  - (a) providing a biological sample from a subject who has received a transplant from a donor, wherein the biological sample comprises nucleic acids from the transplant;
  - (b) determining an amount of nucleic acids from the transplant in the biological sample wherein the determining the amount comprises detecting a polymorphism;
  - (c) comparing the amount of nucleic acids from the transplant to a predetermined

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threshold value, wherein the threshold value is a normative value for clinically stable post-transplantation patients with no evidence of transplant rejection or other transplant pathologies; and

(d) using the comparison of step (c) to detect the transplant condition.

112. (Previously Presented) The method of claim 36, wherein the biological sample is urine.

113. (Currently Amended) The method of claim 61, wherein the detecting of the homozygous or heterozygous SNP comprises using a quality score.

114. (Currently Amended) The method of claim 36, wherein the homozygous or heterozygous polymorphism comprises one or more base changes, an insertion, a repeat, or a deletion.

115. (Currently Amended) The method of claim 36, wherein the homozygous or heterozygous polymorphism comprises a marker having at least two alleles, each occurring at a frequency greater than 1% of the population.

116. (Currently Amended) The method of claim 36, wherein the amount of donor specific cell-free nucleic acids from the transplant in the biological sample is determined in comparison to an amount of reference nucleic acid.

117. (Currently Amended) The method of claim [[56]] 36, wherein the high-throughput sequencing assay comprises mapping one or more of the donor specific cell-free nucleic acids from the transplant in the biological sample with a genome sequence of the donor.

118. (Withdrawn) The method of claim 36, further comprising comparing the amount of cell-free nucleic acids from the transplant to a threshold value.

119. (Withdrawn) The method of claim 118, further comprising using the comparison to detect a transplant condition.



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120. (Currently Amended) The method of claim [119]36, wherein the subject has been treated with an immunosuppressant regimen and further comprising comparing the amount of cell-free nucleic acids from the transplant to a threshold value, using the comparison to detect a transplant condition and, adjusting the immunosuppressant regimen when the transplant condition is detected.
121. (Withdrawn) The method of claim 119, wherein the method detects the transplant condition independent of the gender of the donor or of the recipient.
122. (Currently Amended) The method of claim 36, wherein the donor specific cell-free nucleic acids from the transplant are circulating donor specific cell-free nucleic acids.
123. (Previously Presented) The method of claim 36, wherein biological sample is plasma.
124. (Previously Presented) The method of claim 36, wherein the biological sample is serum.
125. (Previously Presented) The method of claim 64, wherein the immunosuppressant regimen is selected from the group consisting of rapamycin, cyclosporin A, and anti-CD40L monoclonal antibody.
126. (New) The method of claim 36, wherein the method comprises using a computer to access data reflecting the amount of donor-specific cell-free nucleic acids from the solid organ transplant in the biological sample.

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### **REMARKS**

Claims 36-38, 40-55, 57-83, 88, 89, and 91-126 are pending in this application. Claims 1-35, 39, 56, 84-87, and 90 are cancelled. Claims 37, 38, 40-52, 73, 93-111, 118, 119 and 121 are withdrawn. Claims 36, 55, 57, 58, 60-63, 65, 71, 72, 74, 75, 83, 88, 89, 91, 92, 113-117, 120, and 122 are amended herein. Claim 126 is new.

Support for the amendment to claim 36 specifying a solid tumor can be found at claim 39 as filed, and *inter alia*, at [008], [0044] of the published application, US 2015-0337361.

Support for the amendment to claim 36 specifying a homozygous or heterozygous polymorphism can be found *inter alia*, at [0077] of the published application, US 2015-0337361.

Support for the amendment to claim 58 specifying a next generation sequencing assay can be found *inter alia*, at [0084] through [0087] of the published application, US 2015-0337361.

Other amendments to claims 36, 55, 57, 58, 60-63, 65, 71, 72, 74, 75, 83, 88-92, 120, and 122 are made for clarity and appropriate antecedent basis.

Support for new claim 126 can be found, *inter alia*, at [0133] of the published application, US 2015-0337361.

No new matter has been added.

### **Status of withdrawn claims**

In the original restriction response dated April 28, 2016 the Office required restriction between five groups. Applicant elected Group I encompassing claims 36-83, 88, 89, 92, and 112-117 without traverse. Claim 93-111 were withdrawn in response to the restriction requirement. The Office also requested election of species among 16 different genera. Applicant responded with a species election.

In the Office action issued August 11, 2016, the Office stated that claims 37, 38, 40-53, 55, 58, 59, 61-66, 68-70, 73, 74, 76, 77, 79, 81, 92, 112, 113, 115 were withdrawn under 37 C.F.R. 1.142(b). In order to expedite prosecution and without prejudice or disclaimer, Applicant withdraws claims 37, 38, 40-52, 118, 119 and 121 without traverse. All of the remaining pending claims noted as "Previously presented" or "Currently amended" encompass species of the genera previously identified within group I of the April 28, 2016 restriction response. Applicant respectfully submits that upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. See MPEP § 809.02(a).

### **Examiner interview**

Applicant would like to thank the Examiner Amy Bunker, for the interview conducted on September 30, 2016 with Applicant's representative Pamela Sherwood and with Jasemine Chambers, Matt Wheeler, and Kim Stopak, who are all representatives of Applicant's licensee. Claim objections and rejections were discussed as well as potential amendments which are submitted herein. During the interview, the Examiner indicated that the amended claims appear to be allowable but that she would need to perform another search.

### **Claim Objections**

The Office has objected to claim 36. Applicant amends claim 36 herein to recite, "conducting at least one assay, wherein the at least one assay comprises high-throughput sequencing or digital polymerase chain reaction (dPCR)." Applicant requests reconsideration and withdrawal of the objection.

The office has objected to the wording of claim 83. Claim 83 has been amended to recite, "transplant by a factor of two." Applicant requests reconsideration and withdrawal of the objection.

### **Claim Rejections – 35 USC § 112**

The Office has rejected claims 36, 39, 54, 57, 60, 67, 71, 72, 75, 78, 80-83, 88, 89, 91, 114 and 122 are rejected under 35 U.S.C. 112, second paragraph .

Applicant amends claims 36, 71, 72, 75, 89, and 122 to recite, "donor specific cell-free nucleic acids." Applicant requests reconsideration and removal of the rejection.

Applicant amends claim 57 to recite, "the at least one assay is a high-throughput sequencing assay." Applicant requests reconsideration and withdrawal of the rejection.

Applicant amends claim 71 to recite, "a total amount." Applicant requests reconsideration and withdrawal of the rejection.

Applicant amends claim 88 to recite, "wherein [[the]] sensitivity of the method is greater than 56%." Applicant requests reconsideration and withdrawal of the rejection.

Applicant amends claim 89 to recite, "of [[the]] total cell-free nucleic acids in the sample." Applicant requests reconsideration and withdrawal of the rejection.

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### **Claim Rejections – 35 USC § 102**

The Office has rejected claims 36, 39, 54, 57, 60, 67, 72, 75, 78, 80, 114 and 122 under 35 U.S.C. § 102 as allegedly being anticipated by Garritsen et al. (European Patent No. EP 1325963B1, hereinafter “Garritsen”).

Applicant traverses these rejections for at least the following reasons.

#### **Garritsen does not teach or disclose detecting a homozygous or heterozygous polymorphism**

Without conceding the validity of the rejection, and solely to advance prosecution, Applicant has amended claim 36 to recite “wherein determining the amount [of donor specific cell-free nucleic acids] comprises detecting a **homozygous or heterozygous polymorphism** within the donor specific cell-free nucleic acids.” (emphasis added). Garritsen does not teach or suggest a homozygous or heterozygous polymorphism. Instead, Garritsen mentions the use of mitochondrial DNA (mtDNA), which is present in the mitochondria of cells only as a single copy. Therefore, any polymorphism in mitochondrial DNA is hemizygous – **not** homozygous or heterozygous. As such Garritsen fails to anticipate at least this element of independent claim 36, as well as claims 39, 54, 57, 60, 67, 72, 75, 78, 80, 114 and 122, each of which depends from claim 36 and incorporated each and every limitation therein. As such, Applicant requests reconsideration and withdrawal of the rejections of claims 36, 39, 54, 57, 60, 67, 72, 75, 78, 80, 114 and 122 under 35 U.S.C. § 102 based upon Garritsen.

The Office has rejected claims 36, 39, 54, 57, 60, 67, 71, 72, 75, 78, 80-83, 89, 114 and 122 under 35 U.S.C. §102(b) as being allegedly anticipated by Quake et al. (US Patent Application Publication No. 20070202525, published August 30, 2007; hereinafter “Quake”).

Applicant traverses these rejections for at least the following reasons.

**Quake does not teach or disclose “providing a biological sample from a subject who has receive the solid organ transplant from a donor” or “determining an amount of donor specific cell-free nucleic acids from the solid organ transplant”**



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Without conceding the validity of the rejection, and solely to advance prosecution, Applicant has amended claim 36 to recite “providing a biological sample from a subject who has receive the solid organ transplant from a donor,” and, “determining an amount of donor specific cell-free nucleic acids from the solid organ transplant.” Quake refers to analysis of nucleic acids from a fetus. See *e.g.*, at paragraph [0054]. A fetus is not a solid organ transplant. Therefore, Quake fails to anticipate all limitations of independent claim 36 as currently amended, as well as of dependent claims 39, 54, 57, 60, 67, 71, 72, 75, 78, 80-83, 89, 114 and 122. Accordingly, Applicant requests reconsideration and withdrawal of the rejection of claims 36, 39, 54, 57, 60, 67, 71, 72, 75, 78, 80-83, 89, 114 and 122 under 35 U.S.C. §102(b) based upon Quake.

The Office has rejected claims 36, 54, 60, 67, 71, 75 and 122 under 35 U.S.C. § 102(e) as being allegedly anticipated by Lo et al. (US Patent Application Publication No. 20090053719; hereinafter “Lo”).

Applicant traverses these rejections for at least the following reasons.

**Lo does not teach or disclose “providing a biological sample from a subject who has receive the solid organ transplant from a donor” or “determining an amount of donor specific cell-free nucleic acids from the solid organ transplant”**

The Office fails to include claim 39 in its rejection under Lo, which recites, “wherein the transplant is a solid organ.” Nor does the Office allege that Lo teaches, “wherein the transplant is a solid organ.” As currently amended claim 36 incorporates the limitations of claim 39 reciting, “providing a biological sample from a subject who has receive the solid organ transplant from a donor,” and, “determining an amount of donor specific cell-free nucleic acids from the solid organ transplant.” (emphases added). Therefore, Lo fails to anticipate all limitations of independent claim 36 as currently amended, as well as of dependent claims 54, 60, 67, 71, 75 and 122. Applicant thus respectfully requests withdrawal of the rejections under 35 U.S.C. § 102(e) based upon Lo.

### **Claim Rejections – 35 USC § 103**

The Office has rejected claims 36, 39, 54, 57, 60, 67, 71, 72, 75, 78, 80-83, 88, 89, 91, 114 and 122 under 35 U.S.C. §103(a) as being allegedly unpatentable over Garritsen in view of

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Lo; Moyzis et al. (International Patent Application W02008079374A2; hereinafter “Moyzis”) as evidenced by Karger et al. (NIH Public Access Manuscript, 2009, 1-11; hereinafter “Karger”).

Applicant traverses these rejections for at least the following reasons.

As currently amended the claims are directed to a method of detecting donor-specific cell-free nucleic acids in a solid organ transplant recipient, and each and every claim requires:

- providing a biological sample from a subject who has received **the solid organ** transplant from a donor, wherein the biological sample comprises cell-free nucleic acids from the transplant;
- determining an amount of donor specific cell-free nucleic acids from the solid organ transplant in the biological sample;
- wherein determining the amount comprises detecting a **homozygous or heterozygous polymorphism** within the donor specific cell-free nucleic acids from the transplant; and
- conducting at least one assay, wherein the at least one assay comprises high-throughput sequencing or digital polymerase chain reaction (dPCR).

**There is no motivation to combine Garritsen and Lo, given the respective teachings of the references and given that such combination would frustrate the purpose of both Garritsen and Lo**

A person of skill in the art would not be motivated to combine Garritsen with Lo – or, for that matter, Lo with Garritsen – to arrive at the presently claimed invention. The claims, as amended, require, “detecting a **homozygous or heterozygous** polymorphism.” As noted, *supra*, although Garritsen mentions mitochondrial DNA (mtDNA), it fails to disclose a homozygous or heterozygous polymorphism. This is because, in contrast to polymorphisms in nuclear genomic DNA, polymorphisms in mtDNA are **hemizygous** and not **homozygous or heterozygous**. Lo is primarily directed to detecting fetal DNA amongst maternal DNA. Lo also does not disclose detecting mtDNA.

Given the teachings in Garritsen, a person of skill in the art would not be motivated to combine the Garritsen method with a method that does not use mtDNA. Garritsen describes the clear advantage of detecting mtDNA over nuclear DNA, stating, “[mtDNA] is present at over 10[,]000 copies on a per cell basis. This **increases the sensitivity 2-3 logs** when compared to a single copy **nuclear genomic** single nucleotide polymorphism marker.” See paragraph [0013] (emphasis added). Garritsen thus strongly instructs against use of nuclear genomic DNA. Moreover, use of nuclear DNA would defeat the purpose of Garritsen, which intentionally uses mitochondrial DNA in order to boost the sensitivity of the method. ( See MPEP § 2143.01(V), which states “[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).” (emphasis added).

Similarly, a person of skill in the art would not be motivated to combine Lo with Garritsen. Lo is primarily directed to detecting circulating fetal DNA in a maternal host and does not mention detection of nucleic acids from a solid organ transplant. As such, combining Lo with Garritsen would result in a nonfunctional method. This is due to the fact that mtDNA is maternally inherited from mother to child. Therefore, using mtDNA in a method taught by Lo would not allow discrimination between mtDNA derived from the mother and mtDNA derived from the fetus.

Neither Moyzis or Karger can supplement the deficiencies of Lo and Garritsen or provides a motivation to combine the references. Moyzis teaches a method of analyzing SNPs and Karger teaches sequencing methods. Since the combination of Garritsen and Lo would render each unsuitable for their respective intended purposes, the office has failed to establish a *prima facie* case of obviousness. Applicant therefore requests reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) based upon Lo, Garritsen, Moyzis, and Karger.

### **Double Patenting**

The Office provisionally rejected claims 36, 39, 54, 57, 60, 67, 71, 72, 75, 78, 80-83, 88, 89, 91, 114 and 122 on the grounds of alleged nonstatutory obviousness-type double patenting in view of the specification and claims 1, 7, 8 and 16-19 US Patent Application 13/365,240.

Applicant traverses this rejection for at least the following reasons.



Atty Dkt. No.: STAN-706CON  
USSN: 14/188,455

Pending claims of the 13/365,240 application are directed to determining the presence or absence of fetal trisomy 21, and not for, “determining an amount of donor specific cell-free nucleic acids from [a] solid organ transplant in [a] biological sample.” As such the claims are patentably distinct. Applicant thus requests reconsideration and withdrawal of the rejections based on nonstatutory obvious-type double patenting based on claims 1, 7, 8 and 16-19 of US Patent Application 13/365,240.

The Office has rejected claims 36, 39, 54, 57, 60, 67, 71, 72, 75, 78, 80-83, 88, 89, 91, 114 and 122 on the ground of alleged nonstatutory double patenting as being unpatentable over claims 4, 5, 6, 10 and 14 of U.S. Patent No. 8,703,652.

Without agreeing with the Office and merely to expedite prosecution applicant files a terminal disclaimer herein rendering the rejection moot. Applicant thus requests reconsideration and withdrawal of the rejections for nonstatutory obvious-type double patenting based on claims 4, 5, 6, 10 and 14 of U.S. Patent No. 8,703,652.

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of \$3,000.00 beyond that authorized on the credit card, but not more than \$3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number STAN-706CON.

Respectfully submitted,  
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Date: November 11, 2016

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**UNITED STATES DISTRICT COURT**  
**NORTHERN DISTRICT OF CALIFORNIA**

ILLUMINA, INC.,  
  
Plaintiff,  
  
v.  
  
NATERA, INC.,  
  
Defendant.

Case No. 3:18-CV-01662-SI

**DEFENDANT NATERA INC.'S  
NOTICE OF MOTION AND MOTION  
TO DISMISS UNDER FEDERAL  
RULE OF CIVIL PROCEDURE  
12(b)(6)**

Hearing Date: June 22, 2018  
Hearing Time: 9:00 a.m.  
Courtroom: Courtroom 1, 17th Floor  
Judge: Hon. Susan Illston

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**NOTICE OF MOTION AND MOTION**

In accordance with Local Rule 7-2, Defendant Natera, Inc. (“Natera”) hereby provides notice of its Motion to Dismiss under Federal Rule of Civil Procedure 12(b)(6). A hearing on this motion is set for June 22, 2018 at 9:00 a.m. in Courtroom 1 on the 17th Floor of the San Francisco Courthouse: 450 Golden Gate Avenue, San Francisco, California 94102.

Natera respectfully moves the Court to dismiss Illumina, Inc.’s (“Illumina”) Complaint (Dkt. 1) with prejudice for failure to state a claim upon which relief can be granted. As set forth more fully in the accompanying Memorandum of Points and Authorities, the claims of U.S. Patent No. 9,493,831 are not patent-eligible under 35 U.S.C. § 101.

## MEMORANDUM OF POINTS AND AUTHORITIES

### **I. INTRODUCTION**

The claims of U.S. Patent No. 9,493,831 (the “’831 patent”) are not eligible for patenting under 35 U.S.C. § 101 because they are drawn to patent-ineligible—“naturally occurring”—subject matter and describe that ineligible subject matter void of any inventive concept. The ’831 patent claims are directed to a method for preparing a collection, or a “library,” of multiple copies of naturally occurring cell-free fetal and maternal DNA sequences found in a maternal blood sample; the library is prepared using well-known and conventional techniques to copy, or “amplify,” the DNA sequences. While the ’831 patent specification states that the library of DNA sequences may be analyzed for a condition called fetal aneuploidy (where a developing fetus has an abnormal number of chromosomes, and thus is at risk for certain associated genetic disorders), the claims do not require such analysis. The DNA sequences copied and collected according to the ’831 patent claims contain the same genetic information as they do in nature, and are joined in the same complementary fashion as they are in nature. The claims lack an inventive concept because, as the specification confirms, they recite only well-known, routine, and conventional techniques, such as standard amplification processes, to implement the claimed method. The claims also do not provide any unconventional manipulation of, or improvement to, the preexisting technology.

The Supreme Court, the Federal Circuit, and this Court have held ineligible similar claims directed to naturally occurring genetic subject matter. The Supreme Court has held that human DNA is not patent-eligible. *Ass’n for Molecular Pathology v. Myriad*, 133 S. Ct. 2107, 2116–19 (2013). The Federal Circuit and this Court in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 19 F. Supp. 3d 938, 954 (N.D. Cal. 2014), *aff’d*, 788 F.3d 1371, 1377–78 (Fed. Cir. 2015), and the Federal Circuit in *Genetic Technologies Limited v. Merial L.L.C.*, 818 F.3d 1369, 1376–77 (Fed. Cir. 2016), held ineligible claims directed to copying and then analyzing naturally occurring DNA sequences. In fact, the ineligible claims in *Ariosa*, which issued nearly fifteen years *before* the ’831 patent, involved the same naturally occurring cell-free fetal and maternal DNA sequences at issue in this case. Because the ’831 patent claims are directed to a library of DNA sequences, with no detection or analysis, the ’831 patent claims require *even less* than the ineligible claims in *Ariosa* and *Genetic Technologies*.

1 Thus, the claims of the '831 patent do not pass the Section 101 threshold. Illumina's Complaint  
2 accordingly should be dismissed with prejudice.

## 3 **II. BACKGROUND**

### 4 **A. DNA Sequences**

5 Humans have 23 pairs of structures called "chromosomes." *Myriad*, 133 S. Ct. at 2111.  
6 "[P]acked into" these chromosomes are genes, which "form the basis for hereditary traits in living  
7 organisms." *Id.* Humans have "approximately 22,000 genes." *Id.* Each gene consists of  
8 deoxyribonucleic acid ("DNA"), which contains genetic information and "takes the shape of" a  
9 double-stranded structure commonly known as the "double helix." *Id.*

10 Each strand of this DNA "double helix" contains molecules called "nucleotides." *Id.* The four  
11 nucleotides are "adenine (A), thymine (T), cytosine (C), and guanine (G), each of which binds  
12 naturally with another nucleotide: A pairs with T; C pairs with G." *Id.* This complementary binding  
13 "join[s]" the two DNA strands together to form the "double helix." *Id.* Naturally occurring  
14 "[s]equences of DNA nucleotides," such as "AGCTTCTC" (which would complementarily bind to  
15 "TCGAAGAG"), "contain the information necessary to create strings of amino acids, which in turn  
16 are used in the body to build proteins." *Id.*

17 These naturally occurring DNA sequences, which can be found in blood, are the focus of the  
18 '831 patent claims.

### 19 **B. The '831 Patent**

20 The '831 patent issued on November 15, 2016 and claims priority to a provisional application  
21 filed on January 23, 2010. Although the '831 patent is entitled "Methods for Fetal Abnormality  
22 Detection" and the specification discusses detection of fetal aneuploidy, the claims recite no such  
23 detection or other analysis step. '831 patent, 13:29–14:30, 63:38–66:45. Instead, the claims are  
24 limited to copying, without alteration of the genetic information, naturally occurring DNA sequences  
25 found in maternal blood to create a library, *i.e.*, a set of those sequences.

26 The '831 patent has two independent claims—claims 1 and 14; claim 1 is representative of the  
27 '831 patent claims<sup>1</sup>:

28 <sup>1</sup> Courts are free to analyze the patent eligibility of claims together where those claims are  
substantially similar. *See Content Extraction & Transmission LLC v. Wells Fargo Bank, Nat'l*

1 A method for preparing a sequencing library from a maternal blood sample, the method  
2 comprising:

3 a. obtaining a maternal blood sample comprising fetal and maternal cell-free  
4 DNA;

5 b. selectively enriching a plurality of non-random polynucleotide sequences of  
6 genomic DNA from said fetal and maternal cell-free DNA to generate a library  
7 of enriched non-random polynucleotide sequences, wherein said plurality of  
8 non-random polynucleotide sequences comprises at least 100 different non-  
9 random polynucleotide sequences selected from a chromosome tested for being  
10 aneuploid, said enriching comprising:

11 (i) a first amplification step to generate a plurality of first reaction products,  
12 said amplification comprising at least 100 first primers configured to  
13 amplify at least 100 different non-random polynucleotide sequences;

14 (ii) a second amplification step to generate a second reaction product, said  
15 amplification comprising a second set of primers comprising sequences  
16 contained in the first reaction products; and

17 (iii) a third amplification step to generate a third reaction product  
18 comprising said library of enriched non-random polynucleotide sequences,  
19 said amplification comprising a third set of primers comprising sequences  
20 contained in the second reaction products;

21 wherein at least one primer of at least one of the second and third sets of primers  
22 includes a sequence configured to be added to the different non-random  
23 polynucleotide sequences to permit the enriched non-random polynucleotide  
24 sequences of the library to anneal to a same sequencing primer for the enriched  
25 non-random polynucleotide sequences of the library.

26 '831 patent, 63:39–64:42.

27 **The Claims Are Directed to Preparing a Library of Naturally Occurring DNA Sequences.**

28 The '831 patent claims recite a method for preparing a library, or collection, of multiple copies of  
naturally occurring cell-free fetal and maternal DNA sequences found in a maternal blood sample.

The library is prepared using well-known and conventional techniques. This Court previously has  
recognized that such a library is simply a collection or “set of nucleic acid sequences,” *i.e.*, DNA  
sequences. *Aria Diagnostics, Inc. v. Sequenom, Inc.*, No. 3:11-cv-06391, Dkt. 246 (N.D. Cal. Oct. 6,  
2013) (Claim Construction Order) at 41 (“Generate a library . . . ,’ therefore, is construed as ‘generate

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*Ass’n*, 776 F.3d 1343, 1348 (Fed. Cir. 2014) (finding the district court “correctly determined that  
addressing each claim of the asserted patents was unnecessary” because “all the claims are  
‘substantially similar and linked to the same abstract idea’”) (citation omitted).

1 a set of nucleic acid sequences . . . .”) (adopting Verinata’s proposed construction). According to the  
2 claims, the recited library is prepared by obtaining a maternal blood sample, copying DNA sequences  
3 found in the sample, and then collecting those copied sequences. Such libraries, and the techniques  
4 used to prepare such libraries, were well known and conventional in the art, and the ’831 patent does  
5 not recite any new or unknown type of sequencing library. *See* ’831 patent, 14:30–15:22; Ex. A (U.S.  
6 Patent No. 6,632,655), 31:18–32:27 (cited on the face of the ’831 patent and disclosing that “[t]he  
7 construction of nucleic acid libraries of template nucleic acids” was described in the prior art and “well  
8 known”); Ex. B, Fan, H. et al., “Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing  
9 DNA from maternal blood,” PNAS 16266–71 at 16270–71 (Oct. 21, 2008) (“Fan”) (“incorporated by  
10 reference” in the ’831 patent “in [its] entirety”) (at ’831 patent, 7:26–31), and referring to the  
11 conventional preparation of a sequencing library “according to the manufacturer’s protocol with slight  
12 modifications”).

13 **Obtaining a Maternal Blood Sample Through Known Methods.** The ’831 patent claims  
14 recite obtaining a blood sample from a pregnant mother, which typically contains not only the mother’s  
15 DNA but also certain amounts of the fetus’s DNA. ’831 patent, 1:24–28. The claims specify no  
16 particular manner by which to obtain the blood sample, and the specification explains that methods  
17 for doing so “are known in the art.” ’831 patent, 10:23–26.

18 **Selective Enrichment of Naturally Occurring DNA Sequences Known to Be Associated**  
19 **With Fetal Aneuploidy.** The claims also recite “selectively enriching” “non-random polynucleotide  
20 sequences” of the cell-free fetal and maternal DNA in the blood sample. *See, e.g.*, ’831 patent, 63:43–  
21 46. This simply means increasing the concentration or number of pre-selected naturally occurring  
22 DNA sequences, *i.e.*, without alteration of the genetic information, in the maternal blood sample  
23 through well-known methods like amplification (as discussed below). *See* ’831 patent, 5:66–6:14,  
24 6:24–29. Selective enrichment itself is well known and nothing new. *See, e.g.*, Ex. C (U.S. Patent  
25 No. 5,399,491), 1:20–23 (cited on the face of the ’831 patent and disclosing that “[t]he selective  
26 amplification of specific nucleic acid sequences is of value in increasing the sensitivity of diagnostic  
27 and environmental assays while maintaining specificity”); Ex. D (U.S. Patent No. 6,210,891), 9:45–  
28 46 (cited on the face of the ’831 patent and disclosing that “[t]he [claimed] method can be used to both



1 identify and quantitate selectively amplified DNA fragments”); Ex. E (U.S. Patent Publication No.  
2 2009/0087847), ¶ 273 (“incorporated by reference” in the ’831 patent “in [its] entirety” (at ’831  
3 patent, 7:15–32), and disclosing a method by which a “certain sub-population of nucleic acid  
4 sequences from the sample pool is sub-selected or enriched prior to sequencing”).

5 In addition, the specification explains that the copied and collected DNA sequences that will  
6 make up the library are already known in the art to be associated with fetal aneuploidy. ’831 patent,  
7 13:29–61. Illumina did not discover these DNA sequences or natural correlations. For instance, the  
8 specification states that the “non-random polynucleotides that are selectively enriched can be selected  
9 from regions of a chromosome” already “known to have a role in a disease.” ’831 patent, 7:11–14;  
10 *see also id.* at 13:41–14:13.

11 **Use of Known Amplification Methods for Selective Enrichment.** To selectively enrich the  
12 DNA sequences of interest, the claims employ known techniques of amplifying, or making copies of,  
13 the DNA sequences. *See, e.g.*, ’831 patent, 63:43–65.

14 The specification discloses that conventional amplification methods, such as polymerase chain  
15 reaction (PCR), can be used to make copies of the DNA sequences of interest. *See, e.g.*, ’831 patent,  
16 6:44–56, 2:45–46, 9:56–60. PCR generally involves: (1) denaturing, or separating, the double strands  
17 of DNA into single strands; (2) introducing a primer, which is a short, single-stranded DNA sequence  
18 that binds in complementary fashion to the region of a single DNA strand where the sequence of  
19 interest is located, thus serving as the starting point for DNA synthesis in the next step; (3) introducing  
20 a substance or enzyme called polymerase to generate a complementary nucleic acid copy of the DNA  
21 sequence of interest, forming double-stranded DNA once again; and (4) repeating the process (the  
22 “chain reaction”). *Hoffmann-La Roche, Inc. v. Promega Corp.*, 323 F.3d 1354, 1357–58 (Fed. Cir.  
23 2003) (“The polymerase chain reaction (PCR) allows scientists, beginning with a small amount of  
24 deoxyribonucleic acid (DNA), to generate many copies of that DNA in a short period of time.”);<sup>2</sup> *see*

25  
26 <sup>2</sup> *Id.* at 1358 (“In the first stage of PCR, a segment of DNA is *separated* at high temperature into its  
27 two component strands. Then, at a lower temperature, small pieces of synthetic DNA called  
28 ‘*primers*’ are annealed to specific locations on the separated strands. Enzymes known as DNA  
*polymerases* then ‘*extend*’ the primers by attaching a complementary nucleotide to each nucleotide  
in the template strand. In this manner, the polymerase creates two identical double-stranded DNA  
helices from the two separated single strands of the original helix. The process of strand separation,  
primer annealment, and extension is then performed *repeatedly*, resulting in the production of a large



1 also '831 patent, 10:56–11:7. The specification lists several well-known PCR techniques that can be  
2 used to carry out the claimed method, such as “digital PCR (dPCR), quantitative PCR (qPCR), or real-  
3 time PCR (*e.g.*, TaqMan PCR; Applied Biosystems), allele-specific PCR, colony PCR, Hot Start PCR,  
4 in situ PCR (ISH PCR), inverse PCR (IPCR), long PCR, multiplex PCR, or nested PCR.” ’831 patent,  
5 6:44–53.

6 Primers routinely are used in these amplification methods to bind to the regions of a DNA  
7 strand where the DNA sequences of interest are located. To bind to the DNA strand, primers must  
8 have nucleotide sequences complementary to the DNA sequences of interest extracted from the  
9 mother’s blood; as such, these primers include sequences identical to those to which the DNA  
10 sequences of interest bind in nature. *See* ’831 patent, 4:22–33, 8:40–9:10, 3:19–22, 10:1–4, 16:6–8;  
11 *In re BRCA1- & BRCA2- Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755, 758, 760 (Fed.  
12 Cir. 2014) (explaining that primers are “short, synthetic, single-stranded DNA molecule[s] that bind  
13 [] specifically to . . . intended target nucleotide sequence[s]” and “necessarily contain the identical  
14 sequence of the [DNA] sequence directly opposite to the strand to which they are designed to bind”)  
15 (internal quotation marks omitted); *see also Hoffman-La Roche*, 323 F.3d at 1358.

16 It is also routine and conventional in the art to attach to the primers what are known as sequence  
17 “tag[s]” or “indexing sequence[s],” such as those recited in claims 14–16 of the ’831 patent. *See, e.g.*,  
18 ’831 patent, 66:9–20; Ex. F (U.S. Patent No. 8,195,415), 2:19–24 (cited on the face of the ’831 patent  
19 and disclosing that “[a]s is known in the art, the term ‘sequence tag’ refers to a relatively short . . .  
20 nucleic acid sequence that can be used to identify a certain larger sequence.”); Ex. G (U.S. Patent No.  
21 5,695,934), Abstract and 8:59–61 (cited on the face of the ’831 patent and disclosing a “method and  
22 materials for sorting polynucleotides with oligonucleotide tags” and stating that “conditions for  
23 annealing single-stranded or duplex tags to their single-stranded or duplex complements are well  
24 known”). Sequence tags and indexing sequences contain no genetic information—they simply are  
25 used to distinguish the collected DNA sequence copies from each other and as markers to identify the  
26 samples from which the DNA sequences of interest originated, respectively. *See, e.g.*, ’831 patent,  
27 22:22–32, 11:38–48; *see also* Ex. G (U.S. Patent No. 5,695,934), Abstract; Ex. F (U.S. Patent No.

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number of identical DNA strands.”) (emphases added).

8,195,415), 2:19–24; Ex. B, Fan at 16266–67 (referring to the conventional use of sequence tags).

**Other Non-Inventive Limitations.** Certain dependent claims of the ’831 patent, such as claims 6–9, 13, 19–21, and 24, recite limitations relating to the number of DNA sequences of interest to be amplified, the length of their nucleotide bases, the known chromosomes having these DNA sequences, and the known amplification methods to be used. These conventional limitations, however, do not change the fact that the DNA sequences of interest, their nucleotide bases, and the chromosomes having these DNA sequences are themselves naturally occurring. *See, e.g.*, Ex. H (U.S. Provisional Patent Application No. 61/296,358), ¶ 53 (“incorporated by reference” in the ’831 patent “in [its] entirety” (at ’831 patent, 7:18–32), and disclosing amplifying DNA sequences of different base lengths for various numbers of cycles). Nor is the genetic information contained in those sequences different from what exists in nature. And the known amplification techniques used in the claimed method function in their routine and conventional manner regardless of the particular DNA sequences involved.

\* \* \* \* \*

Thus, the claims of the ’831 patent are directed to making copies of and collecting naturally occurring subject matter—cell-free fetal and maternal DNA sequences—using well-known techniques in their routine and conventional manner, without providing any improvement thereto.

### **C. The Complaint**

Illumina filed its Complaint on March 16, 2018, asserting infringement of claims 1–3, 6–10, 13–22, and 24 of the ’831 patent. Dkt. 1. The Complaint contains no factual allegations regarding the eligibility of the claims.

## **III. LEGAL STANDARD**

### **A. Motion to Dismiss Under Rule 12(b)(6)**

Rule 12(b)(6) requires dismissal where a complaint “fail[s] to state a claim upon which relief can be granted.” Thus, “[t]o survive a motion to dismiss, the plaintiff must allege ‘enough facts to state a claim to relief that is plausible on its face.’” *TriDim Innovations LLC v. Amazon.com, Inc.*, 207 F. Supp. 3d 1073, 1077 (N.D. Cal. 2016) (quoting *Bell Atlantic Corp. v. Twombly*, 550 U.S. 544, 570 (2007)).

“In ruling on a 12(b)(6) motion, a court need not ‘accept as true allegations that contradict matters properly subject to judicial notice or by exhibit,’ such as the claims and the patent specification.”<sup>3</sup> *Secured Mail Sol. LLC v. Universal Wilde, Inc.*, 873 F.3d 905, 913 (Fed. Cir. 2017); *see also Tellabs, Inc. v. Makor Issues & Rights, Ltd.*, 551 U.S. 308, 322 (2007) (stating that, in ruling on a motion to dismiss, courts “ordinarily examine . . . matters of which a court may take judicial notice”). A court may take judicial notice of a patent’s prosecution history, which is a public record, in deciding a motion to dismiss. *Genetic Techs Ltd. v. Bristol-Myers Squibb Co.*, 72 F. Supp. 3d 521, 526 (D. Del. 2014) (citing *Hockerson-Halberstadt, Inc. v. Avia Grp. Int’l, Inc.*, 222 F.3d 951, 957 (Fed. Cir. 2000)). Similarly, the Federal Circuit has also “established that ‘prior art cited in a patent or cited in the prosecution history of the patent constitutes intrinsic evidence.’” *V-Formation, Inc. v. Benetton Grp. SpA*, 401 F.3d 1307, 1311 (Fed. Cir. 2005) (quoting *Kumar v. Ovonic Battery Co.*, 351 F.3d 1364, 1368 (Fed. Cir. 2003)). Furthermore, “[w]hen a document is ‘incorporated by reference’ into a . . . patent, the referenced document becomes effectively part of the [patent] as if it were explicitly contained therein,” and is therefore considered “intrinsic evidence” to that patent. *See Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1329 (Fed. Cir. 2001) (quoting *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000)).

### **B. Granting Dismissal on the Basis of Ineligibility**

Courts in this District have granted motions to dismiss on the basis of ineligibility. *See, e.g., TriDim*, 207 F. Supp. 3d at 1080 (dismissing with prejudice); *OpenTV, Inc. v. Apple, Inc.*, No. 14-cv-01622, 2015 WL 1535328, at \*7 (N.D. Cal. Apr. 6, 2015) (same). The Federal Circuit also has “repeatedly affirmed § 101 rejections at the motion to dismiss stage, before claim construction or significant discovery has commenced,” and “based on intrinsic evidence from the specification without need for ‘extraneous fact finding outside the record.’” *See Cleveland Clinic Found. v. True Health Diagnostics LLC*, 859 F.3d 1352, 1360 (Fed. Cir. 2017) (citation omitted); *Secured Mail*, 873 F.3d at 912 (quoting *In re TLI Commc’ns LLC Patent Litig.*, 823 F.3d 607, 613–14 (Fed. Cir. 2016)); *see also Genetic Techs*, 818 F.3d at 1373–74 (“We have repeatedly recognized that in many cases it

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<sup>3</sup> Natera respectfully requests that the Court take judicial notice of Exhibits A through H, as they are part of the ’831 patent’s prosecution history, which is a public record.

1 is possible and proper to determine patent eligibility under 35 U.S.C. § 101 on a Rule 12(b)(6)  
2 motion.”).

3 Recently, the Federal Circuit reiterated that, although patent eligibility is ultimately a legal  
4 question, there may, in some circumstances, be factual disputes underlying the inquiry. In *Aatrix*  
5 *Software, Inc. v. Green Shades Software, Inc.*, 882 F.3d 1121, 1128–29 (Fed. Cir. 2018), the court  
6 held that the particular circumstances of the case rendered it inappropriate to resolve eligibility on a  
7 motion to dismiss. The court held that the patent specification and numerous allegations in the  
8 complaint supported that the claims did not lack an inventive concept and instead recited elements that  
9 were not “well-understood, routine, and conventional.” *Id.* (quoting *Mayo*, 566 U.S. at 73). For  
10 similar reasons, the Federal Circuit in *Berkheimer v. HP Inc.*, 881 F.3d 1360, 1368 (Fed. Cir. 2018),  
11 vacated a grant of summary judgment on the basis of ineligibility. The court in *Berkheimer* stated that  
12 “whether a claim recites patent eligible subject matter is a question of law which *may* contain  
13 underlying facts.” *Id.* (emphasis added). The court, however, made clear that “as [its] cases  
14 demonstrate, *not every* § 101 determination contains *genuine* disputes over the underlying facts  
15 material to the § 101 inquiry.” *Id.* (emphases added).

16 Neither *Aatrix* nor *Berkheimer* apply here because there can be no factual disputes underlying  
17 the eligibility inquiry in this case. See *SAP Am., Inc. v. Investpic, LLC*, No. 2017-2081, 2018 WL  
18 2207254, at \*5 (Fed. Cir. May 15, 2018) (after *Aatrix* and *Berkheimer*, affirming judgment on the  
19 pleadings on the basis of ineligibility, stating that such judgment is proper where “there are no factual  
20 allegations from which one could plausibly infer that [the claims] are inventive”); *Voter Verified, Inc.*  
21 *v. Election Sys. & Software LLC*, 887 F.3d 1376, 1384–86 (Fed. Cir. 2018) (after *Aatrix* and  
22 *Berkheimer*, affirming the grant of dismissal on the basis of ineligibility, and explaining that “[t]he  
23 factual allegations here, taken as true, do not prevent a § 101 determination at the Rule 12(b)(6)  
24 stage”); *Maxon, LLC v. Funai Corp., Inc.*, --- F. App’x ---, 2018 WL 1719101, at \*1–2 (Fed. Cir. Apr.  
25 9, 2018) (same).<sup>4</sup> The ’831 patent specification, for instance, confirms repeatedly that the claims lack

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27 <sup>4</sup> In addition to these written decisions, the Federal Circuit has summarily affirmed grants of dismissal  
28 on the basis of ineligibility. See, e.g., *Mankes v. Fandango, LLC*, No. 2017-1897, 2018 WL 2041560  
(Fed. Cir. May 1, 2018); *Va. Innovation Scis., Inc. v. HTC Corp.*, 718 F. App’x 988 (Fed. Cir. Apr.  
11, 2018); *Dialware Commc’ns, LLC v. Hasbro, Inc.*, 718 F. App’x 974 (Fed. Cir. Apr. 6, 2018);  
*ICON Health & Fitness, Inc. v. Polar Electro OY*, 717 F. App’x 1005 (Fed. Cir. Apr. 4, 2018);

1 an inventive concept and recite only well-known methods functioning in their routine and conventional  
2 manner to make copies of and collect naturally occurring DNA sequences. In addition, the Supreme  
3 Court and the Federal Circuit have held ineligible claims directed to similar subject matter that  
4 required *even more* than simply amplifying and collecting DNA sequences—the subject matter to  
5 which the '831 patent claims are limited.<sup>5</sup> Finally, Illumina's Complaint contains no factual  
6 allegations regarding the eligibility of the claims.

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26 *EveryMd.com LLC v. Facebook Inc.*, 714 F. App'x 1018 (Fed. Cir. Mar. 9, 2018); *Integrated Tech.*  
*Sys., Inc. v. First Internet Bank of Ind.*, 712 F. App'x 1007 (Fed. Cir. Feb. 20, 2018).

27 <sup>5</sup> The Federal Circuit recognized that a “decisional mechanism courts now apply is to examine earlier  
28 cases in which a similar or parallel descriptive nature can be seen—what prior cases were about, and  
which way they were decided.” *Amdocs (Israel) Ltd., v. Opennet Telecom*, 841 F.3d 1288, 1294  
(Fed. Cir. 2016).

### C. The “Threshold Inquiry” for Eligibility Under 35 U.S.C. § 101

The legal question of “[w]hether a claim is drawn to patent-eligible subject matter under § 101 is a threshold inquiry, and any claim of an application failing the requirements of § 101 must be rejected even if it meets all of the other legal requirements of patentability.” *In re Bilski*, 545 F.3d 943, 950 (2008), *aff’d sub nom.*, *Bilski v. Kappos*, 561 U.S. 593 (2010) (citation omitted). The Supreme Court has established a two-step framework for “distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts.” *Ariosa*, 788 F.3d at 1375 (citing *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1297 (2012)); *see also Alice Corp. v. CLS Bank Int’l*, 134 S. Ct. 2347, 2355 (2014).

Under this framework, a court must first “determine whether claims at issue are directed to” one of those “patent-ineligible concept[s].” *Ariosa*, 788 F.3d at 1375. If so, the court must then determine whether the claims contain an “inventive concept,” or “an element or combination of elements that is ‘sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself.’” *Id.* (quoting *Mayo*, 132 S. Ct. at 1294). At this second step, “well-understood, routine, conventional activit[ies]” are insufficient. *Mayo*, 132 S. Ct. at 1294. Because “no presumption of eligibility attends the section 101 inquiry,” *Ultramercial, Inc. v. Hulu, Inc.*, 772 F.3d 709, 717–21 (Fed. Cir. 2014) (Mayer, J., concurring), the “clear and convincing evidence” standard does not apply as it would to invalidity defenses asserted under 35 U.S.C. § 282 based on the presumption of *validity* for issued patents. *Microsoft Corp. v. i4i Ltd. P’ship*, 564 U.S. 91, 102 (2011); *cf. Berkheimer*, 881 F.3d at 1368.

## IV. THE CLAIMS OF THE ’831 PATENT ARE NOT PATENT-ELIGIBLE

### A. Step One: The Claims Are Directed to Naturally Occurring Subject Matter

“[N]aturally occurring” subject matter is “not patentable.” *In re Roslin Inst.*, 750 F.3d 1333, 1336 (Fed. Cir. 2014) (citing, *e.g.*, *Myriad*, 133 S. Ct. at 2107, and *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948)). Here, the claims of the ’831 patent are directed to copying, and collecting in a library, naturally occurring cell-free fetal and maternal DNA sequences.

**The Precedent.** The Supreme Court, the Federal Circuit, and this Court have held that claims directed to naturally occurring subject matter, such as genetic information and copies thereof, are not



1 patent-eligible. For instance, in *Myriad*, the Supreme Court held that claims directed to DNA isolated  
2 from a human’s genome were ineligible because they “did not create or alter any of the genetic  
3 information” contained therein. 133 S. Ct. at 2116. Instead, the Court held, “the location and order  
4 of the nucleotides existed in nature before *Myriad* found them,” and the mere act of “separating [the  
5 DNA] from its surrounding genetic material is not an act of invention.” *Id.* at 2116–17. The Court  
6 did, however, hold as patent-eligible claims directed to cDNA, which were “exons-only molecule[s]  
7 that [were] not naturally occurring” and thus unlike the DNA sequences of interest in the ’831 patent  
8 claims. *Id.* at 2119.

9 Similarly, in *Roslin*, the Federal Circuit held ineligible claims directed to clones of certain  
10 mammals that did not have “markedly different characteristics from the donor animals of which they  
11 [we]re copies.” 750 F.3d at 1339. The court reasoned that, as in *Myriad*, the claims “‘did not create  
12 or alter any of the genetic information’ of [the recited] clones.” *Id.* at 1337 (quoting *Myriad*, 133 S.  
13 Ct. at 2116).

14 In *Ariosa*, this Court held ineligible claims directed to “amplifying” cell-free fetal and maternal  
15 DNA sequences “contained in” a maternal blood sample—the same DNA sequences at issue in this  
16 case—and then “detecting” in that sample “paternally inherited” cell-free fetal and maternal DNA. 19  
17 F. Supp. 3d at 941–42; *Ariosa*, 788 F.3d at 1373, 1376. The Federal Circuit affirmed, holding that the  
18 claims “start[ed]” with “naturally occurring” DNA sequences and “end[ed]” with naturally occurring  
19 DNA sequences, where none “of the genetic information encoded” in the sequences was “created or  
20 altered” in any way. *Ariosa*, 788 F.3d at 1376. Thus, the court explained, the claimed “method . . .  
21 beg[an] and end[ed] with a natural phenomenon” and thus was “directed to matter that is naturally  
22 occurring.” *Id.*

23 Finally, the Federal Circuit in *Genetic Technologies* reached a similar conclusion in upholding  
24 a grant of dismissal on the basis of ineligibility. In *Genetic Technologies*, the court held ineligible  
25 claims directed to “methods of detecting a coding region allele by amplifying and analyzing any linked  
26 non-coding region.” 818 F.3d at 1372–73. The court rejected the patentee’s argument that the claim  
27 at issue was “inventive because it involves analysis of *man-made* amplified DNA,” explaining that  
28 even if the “man-made amplified DNA” had an “altered methylation status,” “its sequence is identical

1 to that of naturally occurring DNA.” *Id.* at 1377 n.3 (internal quotation marks omitted). Thus, because  
2 the claim was “concerned primarily with the information contained in the” naturally occurring “genetic  
3 sequence,” “any minor chemical differences [were] irrelevant.” *Id.* (quoting *Myriad*, 133 S. Ct. at  
4 2118) (internal quotation marks omitted).

5 **The ’831 Patent Claims.** As were the ineligible claims in *Myriad*, *Roslin*, *Ariosa*, and *Genetic*  
6 *Technologies*, the claims of the ’831 patent are directed to naturally occurring subject matter. Like  
7 the claims to isolated DNA in *Myriad*, cloned mammals in *Roslin*, and copies of cell-free fetal and  
8 maternal DNA sequences in *Ariosa*—the same DNA sequences at issue in this case—the ’831 patent  
9 claims do not “create or alter any of the genetic information” contained in the copied DNA sequences  
10 of interest collected in the recited sequencing library. *Myriad*, 133 S. Ct. at 2116; *Roslin*, 750 F.3d at  
11 1337; *Ariosa*, 788 F.3d at 1376. Instead, these DNA sequences and their genetic information already  
12 “existed in nature.” *Myriad*, 133 S. Ct. at 2116; *see also Ariosa*, 788 F.3d at 1376. And as the Federal  
13 Circuit explained in *Genetic Technologies*, that the copied DNA sequences may be “man-made  
14 amplified DNA” does not confer eligibility because, again, the genetic information contained in the  
15 copies is “identical to that of” the naturally occurring DNA sequences. 818 F.3d at 1377 n.3. Because  
16 the claims focus on creating a library of “sequences from a chromosome tested for being aneuploid,”  
17 it is critical that the library contain non-altered DNA sequences that occur naturally; altering the  
18 genetic information would run contrary to the purpose of the claims.

19 Nor does the use of primers in copying these DNA sequences change the fact that the sequences  
20 are naturally occurring. As an initial matter, primers themselves are ineligible. *BRCA1-/BRCA2-*, 774  
21 F.3d at 760. In *BRCA1-/BRCA2-*, the Federal Circuit held that primers, which it described as “short,  
22 synthetic, single-stranded DNA molecule[s] that bind [] specifically to . . . intended target nucleotide  
23 sequences,” are “not distinguishable from the isolated DNA found patent-ineligible in *Myriad*.” *Id.* at  
24 758, 760. The court explained that even if primers are “synthetically replicated,” they nevertheless  
25 are ineligible because they “*necessarily contain the identical sequence* of the [naturally occurring]  
26 sequence directly opposite to the strand to which they are designed to bind.” *Id.* at 760 (emphasis  
27 added). In addition, the court explained, primers “utilize the innate ability of DNA to bind to itself”—  
28 specifically, “that complementary nucleotide sequences bind to each other”—which is “[o]ne of the



1 primary functions of DNA’s structure in nature.” *Id.* at 760–61.

2       Thus, when the DNA sequences of interest bind to the primers, they bind precisely to the  
3 “identical [nucleotide] sequence” to which they would bind in nature by “utiliz[ing] the innate ability  
4 of DNA to bind to itself.” *Id.* at 760–61. In other words, not only do the DNA sequences have the  
5 same genetic information as they would in nature, but they also have the same “innate” function of  
6 binding to complementary nucleotide sequences. This remains true even if sequence tags or indexing  
7 sequences are attached to a primer, as the tags contain no genetic information and do not otherwise  
8 alter the naturally occurring genetic information contained in the DNA sequences of interest. Similar  
9 to the claims in *Genetic Technologies*, the claims of the ’831 patent are “concerned primarily with the  
10 [genetic] information contained in the” naturally occurring DNA sequences of interest (“chromosomes  
11 tested for being aneuploidy”) that are being copied and collected in the recited library. 818 F.3d at  
12 1377 n.3 (quoting *Myriad*, 133 S. Ct. at 2118). Thus, “any minor . . . differences” from nature that  
13 sequence tags or indexing sequences could introduce are “irrelevant” to the ineligibility inquiry. *Id.*  
14 (citing *Myriad*, 133 S. Ct. at 2118). And as discussed further below, sequence tags and indexing  
15 sequences are routine and conventional aspects of the well-known amplification techniques employed  
16 to carry out the claimed method.

17       Finally, the specification of the ’831 patent states that the claimed sequencing library may be  
18 used for fetal aneuploidy detection based on known associated DNA sequences. But the claims—the  
19 focus of the eligibility inquiry—recite no such detection or other analysis steps and are instead limited  
20 to copying and collecting DNA sequences. *Synopsys, Inc. v. Mentor Graphics Corp.*, 839 F.3d 1138,  
21 1149 (Fed. Cir. 2016) (“The § 101 inquiry must focus on the language of the Asserted Claims  
22 themselves”) (citing *Accenture Global Servs., GmbH v. Guidewire Software, Inc.*, 728 F.3d 1336,  
23 1345 (Fed. Cir. 2013)). Regardless, the specification makes clear that Illumina discovered none of the  
24 DNA sequences and their correlations with fetal aneuploidy. Instead, the ’831 patent relies on  
25 preexisting knowledge of that information. ’831 patent, 7:11–14, 13:41–14:13. And in any event,  
26 such correlations are ineligible laws of nature. *See, e.g., Cleveland Clinic*, 859 F.3d at 1360–61  
27 (holding ineligible “methods for observing the law of nature that” heightened levels of the enzyme  
28 myeloperoxidase in the body “correlates to cardiovascular disease”); *Mayo*, 566 U.S. at 73–74, 80

1 (holding ineligible methods applying the law of nature that levels of “certain metabolites” in a patient’s  
2 blood correlates with “the likelihood that a particular dosage of a thiopurine drug could cause harm or  
3 prove ineffective”).

4 Accordingly, the claims of the ’831 patent are directed to copying, and collecting in a library,  
5 naturally occurring cell-free fetal and maternal DNA sequences from a maternal blood sample.

6 **B. Step Two: The Claims Lack Any Inventive Concept**

7 The claims lack any inventive concept that could save them from ineligibility because they  
8 recite no unconventional manipulation of, or improvement to, the preexisting technology.

9 **Well-Known, Routine, and Conventional Techniques.** The ’831 patent claims employ only  
10 “well-known techniques to execute the claimed method.” *Cleveland Clinic*, 859 F.3d at 1361; *see also*  
11 *BRCA1-/BRCA2-*, 774 F.3d at 764 (“Nothing is added by identifying the techniques to be used . . .  
12 because those . . . techniques were the well-understood, routine, and conventional techniques that a  
13 scientist would have thought of”).

14 First, the specification of the ’831 patent makes clear that the first step of obtaining a maternal  
15 blood sample (in which the DNA sequences will be selectively enriched) can be accomplished using  
16 methods that “are known in the art.” ’831 patent, 10:23–26.

17 Second, the specification explains that selectively enriching DNA sequences—regardless of  
18 their number and the length of their nucleotide bases—involves the use of nothing more than well-  
19 known, routine, and conventional amplification techniques, listing several known PCR techniques as  
20 examples. *See, e.g.*, ’831 patent, 6:44–56, 2:45–46, 9:56–60; *see also* Ex. H (U.S. Provisional Patent  
21 Application No. 61/296,358), ¶ 53. The Federal Circuit has held that such amplification techniques  
22 are routine and conventional. *See, e.g., Ariosa*, 788 F.3d at 1377 (holding that recited amplification  
23 and detection steps, which employed “methods like PCR,” were “well-understood, routine, and  
24 conventional activity”); *Genetic Technologies*, 818 F.3d at 1377 (holding that the recited amplification  
25 step, which could be carried out using PCR, “was indisputably well known, routine, and  
26 conventional”); *see also Ariosa*, 19 F. Supp. 3d at 949 (finding that “[s]tandard nucleic acid  
27 amplification systems” like PCR could be used to carry out the claimed method). And as was evident  
28 in *BRCA1-/BRCA2-*, the use of primers is a basic and conventional aspect of these amplification

1 processes. *See* 774 F.3d at 758. So too is the use of attaching sequence tags or indexing sequences to  
2 primers to identify the samples from which the DNA sequences of interest and their copies originated.  
3 *See, e.g.,* '831 patent, 22:22–32, 11:38–48; Ex. G (U.S. Patent No. 5,695,934), Abstract; Ex. F (U.S.  
4 Patent No. 8,195,415), 2:19–24; Ex. B, Fan at 16266–67.

5 Thus, the claims recite only well-known, routine, and conventional elements to implement the  
6 claimed method. This is no surprise, particularly because selective enrichment of DNA sequences and  
7 creating sequencing libraries are themselves nothing new. *See* '831 patent, 8:40–54, 13:41–14:13; Ex.  
8 C (U.S. Patent No. 5,399,491), 1:20–23; Ex. D (U.S. Patent No. 6,210,891), 9:45–46; Ex. E (U.S.  
9 Patent Publication No. 2009/0087847), ¶ 273; Ex. B, Fan at 16270–71; Ex. A (U.S. Patent No.  
10 6,632,655), 31:18–32:27.

11 **No Manipulation of, or Improvement to, the Preexisting Technology.** The claims also  
12 offer no unconventional improvement to the well-known techniques discussed above. They are  
13 distinct from the eligible claims in *Rapid Litigation Management Ltd. v. Cellzdirect*, 827 F.3d 1042  
14 (Fed. Cir. 2016), and in *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals International*  
15 *Limited*, 887 F.3d 1117 (Fed. Cir. 2018).

16 In *Rapid Litigation*, the Federal Circuit held as patent-eligible claims that recited a “new and  
17 improved way of preserving hepatocyte cells for later use,” which provided several “benefits . . . over  
18 the prior art methods,” such as “creat[ing] hepatocyte preparations that no longer exhibit unacceptable  
19 loss of viability” after multiple freeze-thaw cycles and “allow[ing] researchers to pool samples in  
20 advance and preserve them for later use, rather than needing to wait until enough single samples are  
21 accumulated that can be pooled and used immediately.” 827 F.3d at 1048–51. Similarly, in *Vanda*,  
22 the court held as patent-eligible claims reciting a method of treatment that provided ““a new way of  
23 using an existing drug’ that [was] safer for patients” with a specific genotype “because it reduce[d]  
24 the risk of . . . prolongation” of “the time between the Q and T waves of the heart rhythm” typically  
25 associated with the drug. 887 F.3d at 1135–36, 1121 n.2.

26 Here, in contrast, the claims provide no such improvement to, or unconventional manipulation  
27 of, the preexisting technology. For instance, the known amplification methods are used precisely as  
28 intended: to amplify, or copy, the DNA sequences of interest. The recited primers similarly are used

1 for their basic purpose of binding to the complementary nucleotide sequences of denatured DNA  
2 strands and serving as the starting point for DNA synthesis in these amplification processes. Likewise,  
3 sequence tags serve their intended purpose of identifying the samples from which the DNA sequences  
4 and their copies originated, without changing the naturally occurring genetic information of those  
5 sequences. All of these claim elements, which Illumina did not invent, therefore function exactly as  
6 intended, with no improvement thereto. The '831 patent does not even purport to have invented an  
7 improved or unconventional sequence library—it merely claims the creation of a standard collection  
8 of DNA sequences.

9       Instead, the claims are akin to the ineligible claims in *Ariosa* and *Genetic Technologies*—and  
10 the '831 patent claims require *even less* than those ineligible claims. *Ariosa*, 788 F.3d at 1373–74;  
11 *Genetic Technologies*, 818 F.3d at 1377. While the claims in *Ariosa* and *Genetic Technologies*  
12 required *both* amplification of DNA sequences *and* detection of genetic variations in or other analyses  
13 of the amplified sequences, the '831 patent claims recite *only* amplification using routine and  
14 conventional techniques. Indeed, the ineligible claims in *Ariosa* involved the same naturally occurring  
15 cell-free fetal and maternal DNA sequences covered in the '831 patent claims. Thus, if the *Ariosa* and  
16 *Genetic Technologies* claims were ineligible, then the '831 patent claims cannot possibly surpass the  
17 Section 101 “threshold” inquiry either.

18                               \* \* \* \* \*

19       The claims of the '831 patent are not patent-eligible because they broadly cover copying, and  
20 collecting in a library, naturally occurring cell-free fetal and maternal DNA sequences using only well-  
21 known, routine, and conventional techniques, providing no unconventional manipulation or  
22 improvement thereto.

## 23       **V. CONCLUSION**

24       Because the claims of the '831 patent are not patent-eligible under Section 101, Natera  
25 respectfully requests that the Court dismiss Illumina’s Complaint with prejudice.  
26  
27  
28

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Respectfully Submitted,

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**UNITED STATES DISTRICT COURT**  
**NORTHERN DISTRICT OF CALIFORNIA**

ILLUMINA, INC.,  
  
Plaintiff,  
  
v.  
  
NATERA, INC.,  
  
Defendant.

Case No. 3:18-CV-01662-SI

**DEFENDANT NATERA INC.'S  
REPLY IN SUPPORT OF MOTION  
TO DISMISS UNDER FEDERAL  
RULE OF CIVIL PROCEDURE  
12(b)(6)**

Hearing Date: June 22, 2018  
Hearing Time: 9:00 a.m.  
Courtroom: Courtroom 1, 17th Floor  
Judge: Hon. Susan Illston

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1 **I. INTRODUCTION**

2 Illumina's Opposition confirms that the '831 patent is drawn to ineligible subject matter.  
3 Illumina hinges its *Mayo/Alice* step one arguments on the premise that the library constructed  
4 according to the '831 patent method claims is one of synthetic sequences for the purpose of aneuploidy  
5 analysis. *See, e.g.*, Dkt. 32 at 1 (asserting the claims are directed to "an improved method for the  
6 creation of synthetic DNA libraries for aneuploidy analysis"). Putting aside that the claims lack any  
7 analytical requirement, aneuploidy analysis focuses on the naturally occurring genetic information in  
8 the sequences, and not on any "synthetic" components. As a result, under Illumina's own  
9 characterization, the claims are directed primarily to naturally occurring genetic information, and are  
10 not patent-eligible. *Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1377 n.3 (Fed. Cir. 2016)  
11 (quoting *Ass'n for Molecular Pathology v. Myriad*, 133 S. Ct. 2107, 2118 (2013)) (emphasis added).

12 That the '831 patent claims do not modify the naturally occurring genetic information relevant  
13 to aneuploidy detection further confirms the claims' ineligibility. The Supreme Court and the Federal  
14 Circuit consistently have held as ineligible claims that similarly failed to "create or alter any of the  
15 genetic information" in the claimed subject matter. *Myriad*, 133 S. Ct. at 2116; *Ariosa Diagnostics,*  
16 *Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1376 (Fed. Cir. 2015); *Genetic Technologies*, 818 F.3d at 1377  
17 n.3; *In re Roslin Inst.*, 750 F.3d 1333, 1337 (Fed. Cir. 2014). Illumina cannot salvage its claims from  
18 ineligibility by characterizing the DNA sequences as "synthetic" based on the inclusion of  
19 conventional sequencing primer and index sequences assembled via well-known amplification  
20 processes, as these do not alter the naturally occurring genetic information correlated with aneuploidy.

21 Nor does Illumina dispute the '831 patent specification and other intrinsic evidence which, as  
22 Natera explained in its opening brief, confirm that the claims lack an inventive concept. The '831  
23 claims recite a method implementing only the routine and conventional use of well-known technology,  
24 without any unconventional improvement thereto. And while Illumina asserts that the '831 patent  
25 improves upon existing techniques, not once does it support that assertion with a reference to the  
26 patent, the rest of the intrinsic record, or its Complaint. As a result, the '831 patent claims are ineligible  
27 and Natera's motion to dismiss should be granted.<sup>1</sup>

28  

---

<sup>1</sup> *Aatrix Software, Inc. v. Green Shades Software, Inc.*, 882 F.3d 1121 (Fed. Cir. 2018), does not

1 Finally, Illumina’s conditional request for leave to file an amended complaint should be denied.  
 2 The undisputed intrinsic evidence confirms that the claims are ineligible, and Illumina offers no  
 3 material support to the contrary. It would be futile to allow Illumina to file an amended complaint  
 4 with new “factual” allegations that could only contradict, and have no basis in, the ’831 patent and  
 5 intrinsic record. Here, the “flaw lies in” Illumina’s patent “rather than [its] pleading.” *Shortridge v.*  
 6 *Foundation Constr. Payroll Serv., LLC*, 2015 WL 1739256, at \*14 (N.D. Cal. Apr. 14, 2015), *aff’d*,  
 7 655 F. App’x 848 (Fed. Cir. 2016). Leave to amend should be denied.

## 8 **II. THE CLAIMS OF THE ’831 PATENT ARE NOT PATENT-ELIGIBLE**

### 9 **A. Step One: The Claims Are Directed to Naturally Occurring Subject Matter**

10 **According to Illumina, the Claims Are “Concerned Primarily” With the Genetic**  
 11 **Information Contained in the Copied DNA Sequences.** The ’831 patent claims are directed to  
 12 copying, and collecting in a library, naturally occurring cell-free fetal and maternal DNA sequences.  
 13 Dkt. 24 at 12. Illumina does not dispute that the claims cover this subject matter, but embraces this  
 14 point by repeatedly stating that the claimed method is patent-eligible because it is “concerned  
 15 primarily” with preparing DNA libraries that “facilitate aneuploidy detection.” *See, e.g.*, Dkt. 32 at 2,  
 16 7, 17–18. For instance, Illumina argues that the Court’s prior construction of “the ‘selectively  
 17 enriching’ term . . . *to require facilitation of aneuploidy detection*” in a previous litigation somehow  
 18 equates to the “recogni[tion] that the claims of the ’831 patent *expressly include an inventive concept.*”  
 19 Dkt. 32 at 18 (emphasis added). But aneuploidy detection indisputably requires, and fundamentally  
 20 focuses on, analysis of the naturally occurring *genetic information* in the copied DNA sequences to  
 21 detect for such abnormalities. ’831 patent, 13:42–61; Dkt. 24 at 2, 6.

22 In other words, despite lacking any detection step limitations, Illumina makes clear that the  
 23 claims are “concerned primarily with the *[genetic] information* contained in” these copied DNA  
 24 sequences to be analyzed for aneuploidy, rather than “the specific chemical composition of” the

25 preclude dismissal here. In denying rehearing in *Aatrix* and *Berkheimer v. HP Inc.*, 881 F.3d 1360  
 26 (Fed. Cir. 2018), the Federal Circuit explicitly noted that “[n]othing in this decision should be  
 27 viewed as casting doubt on the propriety’ of our previous cases resolving patent eligibility on  
 28 motions to dismiss or summary judgment. Indeed, since *Berkheimer* and *Aatrix*, we have continued  
 to uphold decisions concluding that claims were not patent eligible at these stages.” *Aatrix Software,*  
*Inc. v. Green Shades Software, Inc.*, No. 17-1452, --- F.3d ---, 2018 WL 2436813, at \*3 (Fed. Cir.  
 May 31, 2018) (quoting *Berkheimer*, 881 F.3d at 1368).

1 sequences. *Genetic Techs.*, 818 F.3d at 1377 n.3 (quoting *Myriad*, 133 S. Ct. at 2118) (emphasis  
2 added). The claims are thus akin to those claims that the Supreme Court and the Federal Circuit have  
3 found ineligible.<sup>2</sup> Claims repeatedly have been found ineligible because they were “concerned  
4 primarily with” ineligible subject matter: (1) isolating “the genetic information encoded in the BRCA1  
5 and BRCA2 genes,” which were associated with an “increase” in “risk of developing breast and  
6 ovarian cancer” (*Myriad*, 133 S. Ct. at 2112, 2118); (2) “coding region allele[s],” or forms of genes,  
7 that were “correlated” with certain “genetic disorders and diseases” (*Genetic Technologies*, 818 F.3d  
8 at 1372); and (3) “paternally inherited” cell-free fetal and maternal DNA contained in amplified, or  
9 copied, cell-free fetal and maternal DNA sequences—the same type of sequences at issue here (*Ariosa*,  
10 788 F.3d at 1373, 1376). *See also* Dkt. 24 at 13–14.

11 The ineligible claims in *Genetic Technologies* recited a “method of *detecting* an allele of  
12 interest at a multi-allelic locus . . . by *amplifying* a sequence of non-coding region DNA *known* to be  
13 linked with the allele and then *analyzing* the non-coding region to *detect* the allele.” 818 F.3d at 1374  
14 (emphasis added). The Federal Circuit explained that the claims “broadly cover[ed] essentially all  
15 applications, via standard experimental techniques, of the law of linkage disequilibrium to the problem  
16 of detecting coding sequences of DNA.” *Id.* at 1375. And thus, the court held, the “product of the  
17 [claimed] method” was nothing more than “information about a patient’s *natural* genetic makeup—at  
18 least one coding region allele.” *Id.* (emphasis added). The ’831 patent claims are no different.<sup>3</sup> Like  
19 the ineligible *Genetic Technologies* claims, the ’831 patent claims “broadly cover[.]” “amplifying a  
20 sequence” of “DNA known to be linked with” aneuploidy using “standard experimental techniques,”  
21

22 <sup>2</sup> This Court recently recognized that courts have generally determined whether a patent is directed to  
23 ineligible subject matter by comparing the claims at issue with claims already found ineligible. *See*  
24 *Cave Consulting Group, Inc. v. Truven Health Analytics Inc.*, 2017 WL 6405621, \*5 (N.D. Cal.  
25 2017) (citing *Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327, 1334 (Fed. Cir. 2016)); *see also*  
26 *Amdocs (Israel) Ltd. v. Openet Telecom, Inc.*, 841 F.3d 1288, 1294 (Fed. Cir. 2016) (“[T]he  
27 decisional mechanism courts now apply [for the eligibility analysis] is to examine earlier cases in  
28 which a similar or parallel descriptive nature can be seen—what prior cases were about, and which  
way they were decided.”).

<sup>3</sup> That the ’831 patent claims are directed to a method, as opposed to the DNA itself (Dkt. 32 at 7),  
makes no difference. The ineligible claims in *Mayo*, *Genetic Technologies* and in *Ariosa* were all  
method claims. It is what the claims are directed to, not whether they are method or apparatus,  
which dictates eligibility. Here, the method claims are ineligible because as a whole they are directed  
to copying naturally occurring DNA sequences.

1 and the “product of” the claimed method is “natural genetic” information intended for “detecting”  
2 aneuploidy—what Illumina considers to be the claims’ primary focus.

3 **The Genetic Information Is Identical to What Exists in Nature.** It is undisputed that the  
4 genetic information contained in the copied DNA sequences is not altered from what exists in nature.  
5 This makes sense because, as the ’831 patent specification explains, aneuploidy detection relies on the  
6 analysis of that genetic information in sequences known to be correlated with aneuploidy. ’831 patent,  
7 7:11–14, 13:41–14:13; *see also* Dkt. 24 at 6, 15. Unlike the cDNA held to be patent-eligible in *Myriad*,  
8 here the genetic information remains unaltered. If it were to change, then aneuploidy detection would  
9 be compromised, and Illumina’s identified primary purpose of the claims—to “facilitate aneuploidy  
10 detection”—would be defeated. *See* Dkt. 24 at 14–15; Dkt. 32 at 1. Consequently, the claims cover  
11 nothing more than copying and collecting DNA sequences with genetic information identical to what  
12 exists in nature, just like the ineligible claims to isolated DNA in *Myriad*, cloned mammals in *Roslin*,  
13 copies of cell-free fetal and maternal DNA sequences in *Ariosa*, and copies of DNA sequences in  
14 *Genetic Technologies* that failed to “create or alter any of the genetic information” in the claimed  
15 subject matter. *Myriad*, 133 S. Ct. at 2116; *Roslin*, 750 F.3d at 1337; *Ariosa*, 788 F.3d at 1376; *Genetic*  
16 *Technologies*, 818 F.3d at 1377 n.3; *see also* Dkt. 24 at 12–14.

17 Illumina wholly ignores this issue in its Opposition. Instead, it argues that various, tangential  
18 aspects of the claims—sequencing primer and indexing sequences tacked on to the ends of the  
19 sequences of interest, for instance—confer eligibility. But none of these tack-ons alters the naturally  
20 occurring genetic information in the copied sequences or otherwise presents a material,  
21 unconventional difference in the sequences and preexisting technology that could possibly confer  
22 eligibility:

23 1. **Sequencing Primer and Index Sequences.** Illumina argues that the copied DNA sequences  
24 are “not at all naturally occurring” because the claims recite the use of routinely employed primers  
25 that append to the sequence of interest “either the sequences for a same sequencing primer (claim 1)  
26 and/or an index sequence (claims 2-3 and 14).” Dkt. 32 at 15. Yet in so arguing, Illumina does not  
27 contend that these conventional elements change the naturally occurring genetic information in the  
28 sequences linked to aneuploidy. Likewise, it is undisputed that a sequencing primer and/or index



1 sequence is routinely attached during amplification reactions. For example, the '831 patent explains  
2 that index sequences are used to “distinguish the collected DNA sequence copies from each other and  
3 as markers to identify the samples from which the DNA sequences of interest originated, respectively.”  
4 Dkt. 24 at 7–8 (citing '831 patent, 22:22–32, 11:38–48; *see also*, Ex. G (U.S. Patent No. 5,695,934),  
5 Abstract; Ex. F (U.S. Patent No. 8,195,415), 2:19–24; Ex. B, Fan at 16266–67)); *see also* Dkt. 32 at  
6 15. Thus, they also do not alter the naturally occurring genetic information. As with the ineligible  
7 claims in *Genetic Technologies*, which included “a primer pair,” these conventional elements at most  
8 offer uninventive, “minor . . . differences” that are ultimately “irrelevant” to what Illumina repeatedly  
9 states is the focus of the claims: the genetic information intended to be analyzed for aneuploidy. 818  
10 F.3d at 1377 n.3.

11 Furthermore, even assuming Illumina were correct that use of the sequencing primer and/or  
12 index sequences result in “synthetic” DNA, that alone does not confer eligibility. *See, e.g.*, Dkt. 32 at  
13 1, 2, 5–7, 12–13, 15–16. The Federal Circuit has in several instances rejected this notion. In *Genetic*  
14 *Technologies*, for instance, the Federal Circuit held that the fact that copied DNA sequences were  
15 “*man-made* amplified DNA” did not itself confer eligibility because the genetic information in the  
16 copies was still “identical to that” which exists in nature. 818 F.3d at 1377 n.3 (emphasis added); *see*  
17 *also Ariosa*, 788 F.3d at 1374–76 (holding ineligible claims reciting detection of paternally inherited  
18 DNA in man-made amplified cell-free and maternal DNA). In *Roslin*, the court held ineligible clones  
19 of mammals that had been *artificially* created. 750 F.3d at 1337. Here, like the claims in *Genetic*  
20 *Technologies*, *Ariosa*, and *Roslin*, the '831 patent claims are ineligible even if the copied DNA  
21 sequences may contain “minor chemical differences” that are irrelevant to whether the sequences  
22 reveal aneuploidy, which focuses on the otherwise unaltered, genetic information contained in those  
23 sequences.

24 Finally, as discussed below (*infra*, Section II(B)), Illumina fails to explain how the routine use  
25 of these conventional elements in well-known amplification methods is inventive or provides an  
26 improvement over the prior art. Illumina did not invent the sequencing primer and/or index sequences,  
27 a new type of such elements, or a new way of using them. These conventional elements are instead  
28 used in the claimed method for their intended purposes. *See also* Dkt. 24 at 17–18.

1           2. “Non-Random Distribution”. Illumina further argues that while in nature “cell free fetal  
2 and maternal DNA . . . [is] essentially randomly distributed across all chromosomes in the human  
3 genome,” the claimed method is inventive because it results in “a collection of” DNA sequences “that  
4 are distributed according to a non-natural, non-random pattern.” Dkt. 32 at 16. As an initial matter,  
5 Illumina fails to identify this concept of “non-random distribution” in the claims or to even substantiate  
6 the concept in the intrinsic record, and thus it does not affect the eligibility inquiry. *Synopsys, Inc. v.*  
7 *Mentor Graphics Corp.*, 839 F.3d 1138, 1149 (Fed. Cir. 2016) (“The § 101 inquiry must focus on the  
8 language of the Asserted Claims themselves”) (citing *Accenture Global Servs., GmbH v. Guidewire*  
9 *Software, Inc.*, 728 F.3d 1336, 1345 (Fed. Cir. 2013)). Regardless, such a “non-random distribution”  
10 does not alter the naturally occurring genetic information in the copied sequences; instead, like the  
11 ineligible claims in *Myriad*, it corresponds to “isolating” the naturally occurring DNA sequence so as  
12 to conduct the genetic testing associated with aneuploidy detection. 133 S. Ct. at 2111 (“[W]e hold  
13 that a naturally occurring DNA segment is a product of nature and not patent eligible merely because  
14 it has been isolated”); *see also Funk Bros. Seed Co. v. Kalo Co.*, 333 U.S. 127, 130–32 (1948) (holding  
15 that a new distribution of naturally occurring bacteria strains, which even conferred “an advantage,”  
16 was not patent-eligible where it “produce[d] no new bacteria, no change in the six species of bacteria,  
17 and no enlargement of the range of their utility” and did not “improve in any way [the bacteria strains’]  
18 natural functioning”).

19           3. Comparison to the Ineligible *Ariosa* Claims. The ineligible claims in *Ariosa* recited  
20 amplification of the same, naturally occurring cell-free fetal and maternal DNA sequences covered in  
21 the ’831 patent claims, but, unlike the ’831 patent claims, the *Ariosa* claims required the additional  
22 step of “detecting the presence of a paternally inherited nucleic acid of fetal origin in” those copies.  
23 788 F.3d at 1373, 1376; *see also* Dkt. 24 at 18, 13. Thus, the ’831 patent claims, which require *only*  
24 *amplification* of the same cell-free fetal and maternal DNA sequences and *no detection* step, cannot  
25 possibly be eligible. Dkt. 24 at 18.

26           Illumina, however, argues that the ’831 patent claims “include far more specificity” than the  
27 *Ariosa* claims. Dkt. 32 at 11. But length of a claim does not alone confer eligibility. Although the  
28 ’831 patent claims may contain more words than the *Ariosa* claims, both similarly recite amplification



1 of a desired sequence: “paternally inherited nucleic acid from [a] serum or plasma sample” in the  
2 *Ariosa* claims (788 F.3d at 1373–74), and “non-random polynucleotide sequences . . . from . . . fetal  
3 and maternal cell-free DNA” in the ’831 patent claims (*see, e.g.*, ’831 patent, claim 1). Neither is  
4 more specific than the other.

5 In addition, like the *Ariosa* claims, the ’831 patent claims fail to explain *how* to carry out  
6 amplification of the sequences. *Compare* 788 F.3d at 1373–74, *with* ’831 patent, claim 1. Although  
7 Illumina argues that its claims recite “at least three successive rounds of amplification” (Dkt. 32 at  
8 12), Illumina fails to cite anything in the ’831 patent, intrinsic record, or its Complaint that  
9 demonstrates successive amplification was unconventional or an improvement over prior methods in  
10 a manner sufficient to pass the Section 101 threshold. To the contrary, the ’831 patent and intrinsic  
11 evidence demonstrate that running multiple cycles of amplification to copy DNA sequences was  
12 routine and conventional—evidence that Illumina does not dispute. Dkt. 24 at 8 (citing Ex. H (U.S.  
13 Provisional Patent Application No. 61/296,358), ¶ 53 (“incorporated by reference” in the ’831 patent  
14 “in [its] entiret[y]” (at ’831 patent, 7:18–32), and disclosing amplifying DNA sequences for multiple  
15 cycles)).

16 \* \* \* \* \*

17 The ’831 patent claims are directed to copying, and collecting in a library, naturally occurring  
18 cell-free fetal and maternal DNA sequences. The genetic information in those sequences, which  
19 according to Illumina is the primary concern of the claims in “facilitating aneuploidy detection,”  
20 indisputably is what exists in nature. The claims are ineligible.

21 **B. Step Two: The Claims Lack Any Inventive Concept**

22 Natera has detailed why the ’831 patent claims “as a whole” fail not only step one but also step  
23 two of the eligibility analysis. Dkt. 24 at 3–8, 12–18. At step two, the claims lack an inventive concept  
24 because they cover nothing more than the routine and conventional use of well-known amplification  
25 methods and elements to copy, and collect in a library, naturally occurring DNA sequences, offering  
26 no unconventional improvement to the existing technology. Dkt. 24 at 16–18.

27 **The Undisputed Intrinsic Evidence.** Illumina does not dispute the ’831 patent specification  
28 and intrinsic evidence confirming that claims’ recited elements, both individually and in combination,

1 were well-known, routine, and conventional:

- 2 (1) obtaining a maternal blood sample (Dkt. 24 at 5);
- 3 (2) amplification methods like PCR (Dkt. 24 at 6, 16; *see also Ariosa*, 788 F.3d at 1377;
- 4 *Genetic Technologies*, 818 F.3d at 1377);
- 5 (3) using known amplification methods to “selectively” enrich DNA sequences in blood
- 6 samples (Dkt. 24 at 5, 17);
- 7 (4) carrying out multiple cycles of amplification to copy DNA sequences (Dkt. 24 at 8);
- 8 (5) using primers during amplification to “bind to regions of a DNA strand where the DNA
- 9 sequences of interest are located” (Dkt. 24 at 7, 16–17);
- 10 (6) using primers that contain the sequencing primer sequence and/or an indexing sequence
- 11 during amplification. (Dkt. 24 at 7, 17–18);
- 12 (7) preparing DNA sequencing libraries using known amplification techniques (Dkt. 24 at 5,
- 13 17); and
- 14 (8) the DNA sequences themselves, which contain naturally occurring genetic information
- 15 known to be correlated with fetal aneuploidy (Dkt. 24 at 6, 15).

16 Furthermore, there is no suggestion, in the ’831 patent or elsewhere in the intrinsic record, that  
17 the claim elements, taken individually or as a whole, provide any unconventional improvement to  
18 these preexisting methods and technology. The recited elements in the claimed method are used  
19 precisely for their intended purpose, just as they had been used in the prior art. Dkt. 24 at 17–18.

20 **Illumina’s Contrary Assertions Have No Basis in the Intrinsic Record and Fail as a**  
21 **Matter of Law.** Illumina argues that certain elements of the claimed method are “not routine or  
22 conventional,” but provides no explanation or support. Dkt. 32 at 2, 10. For instance, Illumina points  
23 to nothing in the intrinsic record that supports its assertion that carrying out “at least three successive  
24 rounds of amplification” to copy DNA sequences was unconventional. Nor could it, given the intrinsic  
25 evidence identified above and in Natera’s opening brief. Dkt. 24 at 8 (citing Ex. H). Illumina also  
26 fails to articulate how the recited sequencing primer or index sequences are used unconventionally.  
27 The intrinsic evidence and Illumina instead confirm that such primer and/or index sequences are used  
28 for their intended purpose of facilitating sequencing and to identify the sample from which the DNA

sequence came. Dkt. 32 at 15; *accord* Dkt. 24 at 7–8 and 17–18.

Additionally, Illumina argues, again without citation to anything in the intrinsic record, that the claims provide “improvements,” such as “allow[ing] for aneuploidy *detection* at reduced cost and with potentially improved accuracy and sensitivity,” which apparently met a “need for ‘selectively enriching’ DNA sequences in a manner for aneuploidy analysis.” Dkt. 32 at 1, 7, 18 (emphasis added). But there is no support in the intrinsic record that the ’831 patent’s claimed subject matter actually provides these benefits, and in any event there is “no basis in the *claim[s]*”—the “focus” of the eligibility inquiry—for these purported improvements. They are irrelevant to the analysis. *See Return Mail, Inc. v. U.S. Postal Serv.*, 868 F.3d 1350, 1369 (Fed. Cir. 2017); *Synopsys*, 839 F.3d 1138 (“The § 101 inquiry must focus on the language of the Asserted Claims themselves”) (emphasis added). At bottom, the claimed method merely requires copying naturally occurring sequences using conventional amplification processes for nothing more than their intended purpose: copying.

Finally, Illumina argues that the claims are patent-eligible because they “are tethered to a specific technological realm and do not preempt downstream use of any naturally occurring substance.” Dkt. 32 at 19. The Supreme Court and the Federal Circuit have consistently rejected these arguments as a matter of law. Merely “limit[ing]” subject matter “to a particular technological environment” does not “circumvent[]” the eligibility requirement. *See, e.g., Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 73 (2012); *see also Alice Corp. v. CLS Bank Int’l*, 134 S. Ct. 2347, 2360 (2014). And “[w]hile preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility.” *Ariosa*, 788 F.3d at 1379. Accordingly, “questions of preemption are inherent in[,] . . . resolved,” and “fully addressed” by the two-step “§ 101 analysis,” under which the ’831 patent claims do not pass the Section 101 threshold. *Id.*

\* \* \* \* \*

The claims of the '831 patent are directed to copying, and collecting in a library, naturally occurring DNA sequences. According to Illumina, the claims are patent-eligible because they are “concerned primarily” with preparing DNA sequencing libraries that “facilitate aneuploidy detection.” But aneuploidy detection requires analyzing the *naturally occurring genetic information* in those

1 sequences. As the undisputed intrinsic evidence confirms, the claims lack an inventive concept  
2 because they recite only well-known amplification processes functioning in their routine and  
3 conventional manner, with no inventive improvements. The claims therefore are not patent-eligible,  
4 and Natera's motion to dismiss should be granted.

### 5 **III. ILLUMINA'S REQUEST FOR LEAVE TO AMEND SHOULD BE DENIED**

6 Based on the undisputed intrinsic evidence demonstrating the claims' ineligibility, and in view  
7 of Illumina's failure to identify in its Opposition *any* material support to the contrary, it is evident that  
8 the "flaw lies in" Illumina's patent "rather than [its] pleading." *Shortridge*, 2015 WL 1739256, at \*14  
9 (granting dismissal on the basis of ineligibility and denying leave to amend, stating that "[l]eave to  
10 amend would serve no purpose here because the flaw lies in Shortridge's patent rather than in his  
11 pleading."); *see also Cleveland Clinic Foundation v. True Health Diagnostics LLC*, 859 F.3d 1352,  
12 1363–64 (Fed. Cir. 2017) (affirming a district court's dismissal on the basis of ineligibility and denial  
13 of leave to amend where the intrinsic evidence confirmed that the claims recited only routine and  
14 conventional elements). Thus, "[g]iven the intrinsic evidence (*which cannot change*)," Illumina  
15 "cannot state a plausible claim for infringement of" an eligible patent and permitting Illumina to amend  
16 "would be futile." *TriPlay, Inc. v. WhatsApp Inc.*, No. CV 13-1703-LPS-CJB, 2018 WL 1479027, at  
17 \*8 n.3 (D. Del. March 27, 2018) (granting dismissal on the basis of eligibility) (emphasis added); *see*  
18 *also Maxon, LLC v. Funai Corp., Inc.*, 255 F. Supp. 3d 711, 722 (N.D. Ill. 2017), *aff'd*, No. 2017-  
19 2139, 2018 WL 1719101 (Fed. Cir. Apr. 9, 2018) (granting dismissal with prejudice on the basis of  
20 ineligibility).

21 This is particularly true because Illumina offers no support for its new "factual" allegations,  
22 and thus there is no indication that the allegations could be anything but empty assertions and attorney  
23 argument that could only *contradict* the undisputed intrinsic evidence. *See Cellspin Soft, Inc. v. Fitbit,*  
24 *Inc.*, No. 17-CV-05928-YGR, 2018 WL 1610690, at \*9 (N.D. Cal. Apr. 3, 2018) (granting dismissal  
25 on the basis of ineligibility and holding that "Plaintiff's amended complaints do not change this  
26 conclusion [of ineligibility.] As an initial matter, the Court notes that most of plaintiff's allegations  
27 regarding technological improvements *fail to cite to support in the [asserted] [p]atent.*") (emphasis  
28 added).

1 In addition, Illumina’s reliance on *Aatrix Software, Inc. v. Green Shades Software, Inc.*, 882  
2 F.3d 1121 (Fed. Cir. 2018), to argue that it would not be “futile” to permit an amended complaint must  
3 fail. Dkt. 32 at 20. *Aatrix* held that, under the circumstances of that case, allegations in the complaint  
4 were relevant to inventive concept. *Aatrix*, 882 F.3d at 1126–27; *see also* Dkt. 24 at 10–11. Unlike  
5 Illumina, the patentee in *Aatrix* offered a proposed amended complaint that contained a section entitled  
6 “Improvements and Problems Solved by the Aatrix Patented Inventions.” Ex. I (Aatrix Proposed  
7 Second Amended Complaint) at 41–44.

8 Illumina presumably knew of *Aatrix*, which issued on February 14, 2018—a month before  
9 Illumina filed its Complaint on March 16, 2018. On February 22, 2018, in successfully opposing a  
10 motion to dismiss on the basis of ineligibility in *Pacific Biosciences of California v. Oxford Nanopore*  
11 *Technologies, Inc.*, No. 1:17-cv-01353-LPS (D. Del.), Illumina’s counsel filed a Notice of Subsequent  
12 Authority summarizing *Aatrix*, arguing it was “*directly relevant* to at least the *express allegations . . .*  
13 *regarding inventive concept*” in their client’s First Amended Complaint. Ex. J (*Pacific Biosciences*,  
14 No. 1:17-cv-01353-LPS, Dkt. 36 (D. Del. Feb. 22, 2018)) at 1–2.

15 Nevertheless, a month later Illumina and this same counsel filed the Complaint in this action,  
16 *devoid of any allegations* regarding inventive concept. Dkt. 1. Having ignored *Aatrix* before filing its  
17 Complaint, Illumina should not now be allowed to take advantage of the decision in an attempt to cure  
18 its deficient pleading with allegations that could not possibly have any basis in the ’831 patent and  
19 intrinsic record. Leave to amend should be denied.

#### 20 **IV. CONCLUSION**

21 Because the ’831 patent claims are not patent-eligible under Section 101, and because it would  
22 be futile to allow Illumina to amend its complaint, Natera respectfully requests that the Court dismiss  
23 Illumina’s Complaint with prejudice and deny Illumina’s conditional request for leave to amend.  
24  
25  
26  
27  
28

Respectfully Submitted,

Dated: June 7, 2018

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# **EXHIBIT 7**

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

CAREDX, INC. and THE BOARD OF	)	
TRUSTEES OF THE LELAND	)	
STANFORD JUNIOR UNIVERSITY,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	C.A. No. 19-567 (CFC) (CJB)
	)	CONSOLIDATED
NATERA, INC.,	)	
	)	
Defendant.	)	

**NATERA, INC.’S MOTION TO DISMISS PURSUANT TO FEDERAL  
RULE OF CIVIL PROCEDURE 12(b)(6)**

Pursuant to Federal Rule of Civil Procedure 12(b)(6), Defendant Natera, Inc. (“Natera”) moves to dismiss all counts of Plaintiffs CareDx, Inc. and The Board of Trustees of the Leland Stanford Junior University’s First Amended Complaint for failure to state a claim upon which relief can be granted. The grounds for this motion are set forth in Natera’s Opening Brief, submitted herewith.



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**CERTIFICATE OF SERVICE**

I hereby certify that on April 9, 2020, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on April 9, 2020, upon the following in the manner indicated:

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# **EXHIBIT 8**

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

CAREDX, INC. and THE BOARD OF	)	
TRUSTEES OF THE LELAND	)	
STANFORD JUNIOR UNIVERSITY,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	C.A. No. 19-567 (CFC) (CJB)
	)	CONSOLIDATED
NATERA, INC.,	)	
	)	
Defendant.	)	

**NATERA INC.'S OPENING BRIEF IN SUPPORT OF ITS MOTION TO  
DISMISS PURSUANT TO FEDERAL RULE OF CIVIL PROCEDURE  
12(b)(6)**

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## I. NATURE AND STAGE OF THE PROCEEDINGS

CareDx, Inc. and The Board of Trustees of the Leland Stanford Junior University filed a First Amended Complaint (“FAC”) against Natera, Inc. (“Natera”) (D.I. 74) on March 12, 2020. The FAC alleges that Natera’s Kidney Transplant Rejection Test infringes U.S. Patent Nos. 8,703,652 (“652 patent,” Ex. A),<sup>1</sup> 9,845,497 (“497 patent,” Ex. B), and 10,329,607 (“607 Patent,” Ex. C, and collectively the “Patents”). Pursuant to Fed. R. Civ. P. 12(b)(6), Natera moves to dismiss the FAC because the Patent claims are unpatentable under 35 U.S.C. § 101.

## II. SUMMARY OF THE ARGUMENT

The Patent claims focus on detecting what the Patents refer to as a natural phenomenon: cell-free DNA (“cfDNA”) from a transplanted organ that circulates in the blood of a transplant recipient. But “laws of nature, natural phenomena, and abstract ideas are not patentable.” *Mayo Collaborative Servs. v. Prometheus Labs, Inc.*, 566 U.S. 66, 70 (2012). Beyond that, the patents concede the claims recite only conventional techniques for detecting this natural phenomenon. But that fails to render the claims patentable because such claims “only encompasses the natural law itself.” *Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 915 F.3d 743, 752-53 (Fed. Cir. 2019). No further amendment can cure these defects.

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<sup>1</sup> “Ex.” refers to exhibits to the Declaration of Sandra L. Haberny, filed herewith.



Accordingly, the FAC should be dismissed with prejudice.

### III. STATEMENT OF FACTS

Deoxyribonucleic acid (“DNA”) is a “nucleic acid” that serves as a unique molecular blueprint.<sup>2</sup> It is made up of building blocks called “nucleotides” that are strung together in a particular “sequence.” These sequences comprise the genetic makeup or “genotype” of an individual, and variations in this sequence (“polymorphisms,” “single nucleotide polymorphisms,” or “SNPs”) account for differences between individuals, including differences between a transplant donor and recipient. *See* Ex. A, at 11:24-26.<sup>3</sup>

DNA is typically found inside the cells of an individual, but when those cells die (via a process called “apoptosis”) their DNA is broken up and released to freely circulate in the blood as cfDNA. *Id.* at 6:57-67; 7:40-46. The circulating cfDNA in a transplant recipient includes DNA from the transplant recipient and DNA from the donor organ (“donor-specific” cfDNA). *Id.* at 7:37-46. The circulating cfDNA in a transplant recipient can be traced to the recipient or to the donor organ based on the naturally occurring differences in their genetic polymorphisms, or SNPs.

The amount of donor-specific cfDNA circulating in a patient who receives

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<sup>2</sup> The pertinent properties of nucleic acids, such as DNA, are well-understood. *See Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 582 (2013).

<sup>3</sup> A person inherits two copies of genetic information (including SNPs) - one from the mother and one from the father. If the copies are the same, they are considered “homozygous.” If the copies are different, they are considered “heterozygous.”

an organ transplant correlates to the likelihood of the transplant's failure. The more donor-specific cfDNA there is circulating in a patient's blood, the more cell death there is occurring in the transplanted organ. The greater the occurrence of cell death in the transplanted organ, the greater the likelihood of organ failure.

#### **A. The Patent Claims**

The Patent claims<sup>4</sup> are directed to detecting donor-specific cfDNA circulating in a transplant recipient, and in the case of the '652 Patent, correlating that to transplant failure. Claim 1 of the '652 patent recites “[a] method for *detecting transplant rejection ... or organ failure.*” Claim 1 of the '497 patent recites “[a] method of *detecting donor-specific circulating cell-free nucleic acids in a solid organ transplant recipient.*” And claim 1 of the '607 patent recites “[a] method of *quantifying kidney transplant-derived circulating [cfDNA] in a human kidney transplant recipient.*” These claims all recite using the following techniques for this detection and correlation:

- **Obtaining/providing a biological sample containing cfDNA from a transplant recipient**
  - See '652 Patent Claim 1(a) (“providing a sample comprising [cfDNA]”)<sup>5</sup>

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<sup>4</sup> The Patents have a common written description, and one independent claim each.

<sup>5</sup> '652 patent claims 3 and 12-16 recite similar sampling and transplant-related limitations.

- See '497 Patent Claim 1(c) (“obtaining a biological sample”)<sup>6</sup>
- See '607 Patent Claims 1(a) and (b) (“providing a plasma sample” and “extracting circulating [cfDNA]”)
- **Genotyping the transplant donor and/or recipient to establish profiles of genetic polymorphisms (or SNPs or distinguishable markers)**
  - See '652 Patent Claim 1(b) (“obtaining a genotype ... to establish a polymorphism profile”)<sup>7</sup>
  - See '497 Patent Claims 1(a) and (b) (“genotyping ... to obtain a SNP profile”)<sup>8</sup>
  - See '607 Patent Claim 1(c) (“performing a selective amplification of [SNPs] ... by [PCR]”); Claim 1(f) (“using markers distinguishable between said [recipient and donor] [that] comprise [SNPs]”)<sup>9</sup>
- **Performing multiplex or high-throughput sequencing of the cfDNA to detect the genotyped polymorphisms (or SNPs or distinguishable genetic markers)**
  - See '652 Patent Claim 1(c) (“multiplex sequencing of the [cfDNA] in the sample followed by analysis of the sequencing results using the polymorphism profile”)<sup>10</sup>
  - See '497 Patent Claim 1(d) (“determining an amount of donor-

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<sup>6</sup> '497 patent claims 2, 9, 12-14, 27, and 28 recite similar sampling and transplant-related limitations.

<sup>7</sup> '652 patent claims 2 and 11 recite similar genotyping and polymorphism-related limitations.

<sup>8</sup> '497 patent claims 6, 15-18, 24, and 25 recite similar genotyping and polymorphism-related limitations.

<sup>9</sup> '607 patent claims 2-5 recite similar genotyping and polymorphism-related limitations.

<sup>10</sup> '652 patent claims 4-6, and 10 recite similar sequencing-related limitations.

specific [cfDNA] by ... high-throughput sequencing or [dPCR]”)<sup>11</sup>

- See ’607 Patent Claims 1(d-e) (“performing a high throughput sequencing reaction ... compris[ing] ... sequencing-by-synthesis ... [and] ... providing sequences from said high throughput sequencing reaction”)<sup>12</sup>

- **Quantifying the transplant cfDNA in the sample using the genetic differences in the sequences**

- See ’652 Patent Claim 1(d) (“determining a quantity of [transplant cfDNA] based on the detection of [donor and recipient cfDNA] by the multiplexed sequencing”)
- See ’497 Patent Claim 1(d) (“determining an amount of [transplant cfDNA] ... by detecting a homozygous or a heterozygous SNP within the [transplant cfDNA]”)
- See ’607 Patent Claim 1(f) (“quantifying an amount of [transplant cfDNA] ... using markers distinguishable between ... recipient and ... donor”)

#### IV. LEGAL STANDARD

Only “innovative” or “inventive” uses of natural phenomena are afforded patent protection. *Myriad*, 569 U.S. at 595. Thus, Courts ask two questions in determining whether patent claims reciting natural phenomena are eligible for protection under 35 U.S.C. § 101: (1) whether the patent is directed to the natural phenomenon, and if so, (2) whether the claims recite an inventive concept “sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself.” *Mayo*, 566 U.S. at 72-73, 77-80; *Ariosa*

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<sup>11</sup> ’497 patent claims 3-5, 10, 11, 26, and 30 recite similar sequencing-related limitations.

<sup>12</sup> ’607 patent claim 6 recites similar sequencing-related limitations.

*Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1375 (Fed. Cir. 2015).

A Section 101 motion to dismiss is proper if it is apparent from the patent that the asserted claims are not directed to eligible subject matter. *Berkheimer v. HP Inc.*, 881 F.3d 1360, 1368 (Fed. Cir. 2018); *Cleveland Clinic Found. v. True Health Diagnostics LLC*, 859 F.3d 1352, 1360 (Fed. Cir. 2017). And a court need not individually address claims not identified by the non-moving party if the court identifies a representative claim and “all the claims ‘are substantially similar and linked to the same abstract idea.’” *Content Extraction & Transmission LLC v. Wells Fargo Bank, Nat. Ass’n*, 776 F.3d 1343, 1348 (Fed. Cir. 2014) (citations omitted).

## V. ARGUMENT

### A. The Claims Of The Patents Are Directed To Natural Phenomena And Recite No Patent-Eligible Application

To determine patent eligibility, a court must “determine whether the claims at issue are directed to [a] patent-ineligible concept[.]” *Alice Corp. Pty. Ltd v. CLS Bank Int’l*, 573 U.S. 208, 217 (2014). If the patents recite a natural phenomenon with no “additional elements [that] transform the nature of the claim into a patent-eligible application,” then they are not patent-eligible under Section 101. *Id.*

Claims “directed to detecting the presence of a naturally occurring thing or a natural phenomenon” using only “well-understood, routine, and conventional”

techniques are uniformly found not to be patent-eligible. *Ariosa*, 788 F.3d at 1376-77; *see* section V.B below. Here, it is clear that the claims of the '497 and '697 Patents are directed to detecting a natural phenomenon—cfDNA from a transplanted organ that circulates in the blood of a transplant recipient—using only conventional techniques. It is also clear that the claims of the '652 Patent are directed to using the quantities of those cfDNA to correlate to transplant health. Supreme Court and Federal Circuit precedent dictate that this is not patent eligible.

### **1. The Patents Describe The Claims' Focus As A Natural Phenomenon**

The Patents themselves concede that the cfDNA detected by the claimed methods occurs naturally as a result of cell death in a transplant recipient's body. Ex. A, at 6:61-64; 7:40-46 (“[A]s cell-free DNA or RNA often arises from [dying] cells, the relative amount of donor-specific sequences in circulating nucleic acids should provide a predictive measure of on-coming organ failure in transplant patients...”). The Patents further describe cell death, and the consequent release of cfDNA, as something that naturally occurs more frequently when a transplant is failing. *Id.* at 7:40-46; 8:18-21.

### **2. The Claims Recite Only Standard, Unimproved Techniques For Detecting Or Quantifying Donor-Specific cfDNA**

Claims that involve “detecting a natural law ‘with no meaningful non-

routine steps” are “directed to” that natural law. *Athena*, 915 F.3d at 752 (quoting *Cleveland Clinic*, 859 F.3d at 1361). Because the Patents’ claims are directed to detecting naturally occurring donor-derived cfDNA using only routine steps, they are unpatentable. Indeed, the patents themselves repeatedly admit the conventionality of their recited methods. For the Court’s convenience, Exhibit D includes a table of excerpts from the Patents reproducing the cited disclosures below.

At the threshold, the Patents establish that “[t]he *practice of the present invention employs, unless otherwise indicated, conventional techniques ... which are within the skill of the art.*” Ex. A, at 5:36-48.<sup>13</sup> The Patents identify each claimed step as “conventional,” without “otherwise indicate[ing]” that any step is beyond the ordinary skill. No improvements to any of these techniques are recited anywhere in the record. Instead, the Patent claims recite a standard combination of:

- obtaining a biological sample that contains transplant cfDNA;
- genotyping the transplant donor and/or recipient to establish profiles of genetic polymorphisms (or SNPs or distinguishable markers);
- performing multiplex or high-throughput sequencing of the cfDNA to detect the genotyped polymorphisms (or SNPs or distinguishable genetic markers); and

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<sup>13</sup> All emphases are added unless otherwise noted.

- using the polymorphisms (or SNPs or distinguishable genetic markers) to quantify the transplant cfDNA in the sample.

This is a standard way of detecting sequences, such as in donor-specific DNA, that differ from a patient's normal genotype. The Patents recount numerous "applications of circulating nucleic acids, [in which] the presence of sequences differing from a patient's normal genotype has been used to detect disease." *Id.* at 7:30-32; 6:67-7:29; 7:40-46; 8:18-21. They explain that polymorphisms including SNPs were routinely used for differential detection and quantification, highlighting that "any donor and recipient will vary at roughly three million SNP positions if fully genotyped." *Id.* at 13:42-44' 16:3-7.

These variations are readily assessed from a biological sample containing cfDNA, but the Patents do not recite any improvements for "***obtaining***" or "***providing***" such a sample. Rather, the patents state that "[t]o obtain a blood sample, any technique known in the art may be used..." *Id.* at 10:11-12; *id.* at 1:14-17; 6:57-67; 9:4-14; 10:7-10.

The claimed "***genotyping***" was also well-known, with the Patents noting that "[g]enotyping of the transplant donor and/or the transplant recipient may be performed by any suitable method known in the art including those described herein such as sequencing ... or PCR." *Id.* at 20:31-37; 13:51-67; 20:31-51; 26:38-41. The related concept of '607 element 1(c), "***selective amplification***" to



***“amplify] ... at least 1,000 [homozygous and heterozygous SNPs] ... by PCR,”***

is also described in the Patents, *e.g.*, at *id.* at 13:55-67, as a routine technique that scientists perform using off-the-shelf products:

Usable SNPs may comprise approximately 500,000 heterozygous<sup>14</sup> donor SNPs and approximately 160,000 homozygous donor SNPs. Companies ... currently offer both standard and custom-designed TaqMan probe sets for SNP genotyping that can in principle target any desired SNP position for a PCR-based assay .... With such a large pool of potential SNPs to choose from, a usable subset of existing or custom probes can be selected to serve as the probe set for any donor/recipient pair.

The Patents likewise describe obtaining and using the ***“polymorphism” or “SNP” “profile”*** of ’652 element 1(b) and ’497 elements 1(a) and (b), or ***“using markers distinguishable between [recipient and donor] ... compris[ing] [SNPs]”*** of ’607 element (f), as standard, noting that “after genotyping a transplant donor and transplant recipient, using existing genotyping platforms know [sic] in the art including the one described herein, one could identify approximately 1.2 million total variations between a transplant donor and transplant recipient.” *Id.* at 13:51-55. The Patent claims recite no improvements over these established approaches to genotyping and polymorphism/SNP profiling.

Regarding ***“multiplex”*** and ***“high-throughput sequencing,”*** the Patents list numerous established commercial providers, *id.* at 15:22-67; 16:58-17:3, and

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<sup>14</sup> An individual inherits a set of genes from its mother and another from its father. An individual is “homozygous” at a SNP locus when the nucleotide sequences it inherited from mother and father are the same there. An individual is “heterozygous” when the sequences inherited from mother and father differ there.

incorporate literature describing the standard use of these techniques. *Id.* at 15:53-17:14; *see also id.* at 7:23-28; 9:8-14; 14:58-67; 15:22-17:14; 21:5-8.

The Patents also describe “*quantifying*” or “*determining an amount*” of transplant cfDNA, noting that “[d]etection, identification, and/or quantification of the donor-specific markers (e.g., polymorphic markers such as SNPs) can be performed using [numerous techniques]... as well as other methods known in the art including the methods described herein.” *Id.* at 9:8-14; 17:41-18:53; 18:56-19:2 (“Methods for quantifying nucleic acids are known in the art...”); 21:5-9.

The final sensitivity limitation of the ’652 patent, wherein “*sensitivity of the method is greater than 56% compared to sensitivity of current surveillance methods for ... CAV*” is also conventional. Assuming for purposes of this motion that this limitation is not indefinite, it would refer to a degree of sensitivity inherent in the conventional methods of the claims. The Patents disclose standard ways to achieve higher sensitivities and lower error rates using the commercially available sequencing equipment referenced therein. *Id.* at 17:12-15; 17:22-25.

The final portions of ’497 element 1(d) and ’607 element 1(f) are also conventional for similar reasons.<sup>15</sup> Each recites detection wherein donor-specific cfDNA is “*at least 0.03% of the total circulating [cfDNA] in the biological sample.*” This detection threshold describes nothing more than an inherent property

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<sup>15</sup> ’497 patent claims 19-23, and 31-33 and ’607 patent claims 7-10 recite similar cfDNA concentration limitations.

of the commercially available sequencing equipment described in the Patents, which can detect “donor molecules when the donor fraction is as low as 0.03%.” Ex. A at 17:1-3; 17:7-11. The ’607 Patent recitation of a “***sequencing error rate of less than 1.5%***” is likewise just an inherent property of the commercial sequencers readily available at the time. *Id.* at 16:20-21. As such, these sensitivity limitations do not recite any improvement over standard technologies disclosed in the written description. Instead, they refer only to sensitivity inherent in the off-the-shelf sequencers disclosed in the patent.

Accordingly, the Patents concede that the recited methods for obtaining biological samples, genotyping, sequencing, and detecting or quantifying cfDNA were standard and commercially available as of the time the Patents were filed. The Patents’ claims recite no improvements over these standard methods, and thus, the claims “only encompasses the natural law itself.” *Athena*, 915 F.3d at 752-53.

### **3. The Claims As A Whole Recite No Inventive Concept That Would Transform Them Into A Patent-Eligible Application**

Even combining the conventional steps described above, there is no inventive concept “sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself.” *Mayo*, 566 U.S. at 73. “To save a patent” under *Alice/Mayo*, “an inventive concept ‘must be evident in the claims.’” *Whitserve LLC v. Dropbox, Inc.*, No. 18-665-CFC, 2019 WL 3342949, at \*5 (D. Del. July 25, 2019) (quoting and citing *Two-Way Media Ltd. v.*

*Comcast Cable Commc'ns, LLC*, 874 F.3d 1329, 1338 (Fed. Cir. 2017)). Here, the claims as a whole here describe nothing inventive. The Patents do not suggest that the recited combinations of method steps are inventive in any way.

Indeed, the Patent claims recite only unimproved applications of previously used combinations for detecting and quantifying abnormal cfDNA using genotyping (including of SNPs) by PCR, and high throughput or multiplex sequencing. The Patents describe this combination as well-known for diagnosing other conditions such as fetal conditions and cancer. Ex. A at 6:57-7:46. As the Patents explain:

*In all these applications of circulating nucleic acids, the presence of sequences differing from a patient's normal genotype has been used to detect disease.* In *cancer*, mutations of genes are a tell-tale sign of the advance of the disease; in *fetal diagnostics*, the detection of sequences specific to the fetus compared to maternal DNA allows for analysis of the health of the fetus.

*Id.* at 7:30-36. Prior publications that the Patents incorporate by reference also disclose this combination as well-understood and previously used in the art. One example is U.S. Pat. App. No. 2009/0221620 (“Luke”), Ex. G. Luke discloses the same technique using a standard combination of:

- **Obtaining or providing a biological sample containing cfDNA from a transplant recipient:** *Id.* at ¶ 0155 (describing routine sample collection);
- **Genotyping the donor and/or recipient to establish genetic profiles:** *Id.* at ¶¶ 0027; ¶¶ 0031; *id.* at ¶ 0320; *id.* at ¶ 0035 (using commercially

available “kits comprising SNP detection reagents,”); *id.* at ¶ 0209 (commercially available kits can detect “at least 1; 10; 100; 1000; 10,000; 100,000” or more SNPs);

- **Performing multiplex or high-throughput sequencing of the cfDNA to detect the genetic differences:** *Id.* at ¶ 0241 (describing detecting SNPs in samples containing cfDNA “by methods well known in the art” including “pyrosequencing,” a method of sequencing by synthesis); *id.* at ¶ 0252 (describing studies and “commercial instrumentation” for using “high-throughput SNP analysis”);
- **Quantifying the transplant cfDNA in the sample using the genetic differences in the sequences.** *Id.* at ¶ 154; *id.* at ¶ 284 (regarding hetero- and homozygosity of SNPs, “[i]t is now common place to directly observe genetic variants in a sample of chromosomes obtained from a population).

The claims of the Patents differ from Luke only in the polymorphisms they select, and the clinical indication they assess (here, organ transplant rejection). Applying this well-known combination, as exemplified by the Patents, Luke, and others, to the natural phenomenon of donor-specific cfDNA in transplant patients does not in itself create an inventive concept. *See, e.g., Molecular Pathology*, 689 F.3d at 1334.

## **B. The Claims Do Not Become Patentable Simply By Limiting The Field Of Use**

“As the Supreme Court has held, ‘the prohibition against patenting abstract ideas [or natural phenomena] cannot be circumvented by attempting to limit the use of the formula to a particular technological environment.’” *Ass’n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1334 (Fed. Cir. 2012) (citing *Bilski v. Kappos*, 561 U.S. 593, 610 (2010)) (finding that “[l]imiting [a] comparison ... to just the BRCA genes or ... the identification of particular alterations,” *i.e.*, particular manifestations of natural phenomena regarding genetic mutations, “fails to render the claimed process patent-eligible.”). Here, the only purportedly new feature of the claims is an attempt to limit known and standard cfDNA detection / quantification methods to the field of use of **transplant** cfDNA. That is insufficient to render the claims patentable.

Numerous other courts have found that limiting the field of use of conventional techniques to specific categories of natural phenomena—like the donor-specific category of cfDNA here—is insufficient to confer patentability.<sup>16</sup> *Genetic Techs.* and *Ariosa* are particularly analogous. In both cases, the Federal Circuit held that various “physical steps” such as the “physical steps of DNA amplification and analysis of the amplified DNA” and “PCR to amplify and detect

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<sup>16</sup> See, e.g., *Alice*, 573 U.S. at 222-23; *Mayo*, 566 U.S. at 84; *Bilski*, 561 U.S. at 612; *Affinity Labs of Texas, LLC v. DIRECTV, LLC*, 838 F.3d 1253, 1259 (Fed. Cir. 2016); *Content Extraction*, 776 F.3d at 1348; *buySAFE, Inc. v. Google, Inc.*, 765 F.3d 1350, 1355 (Fed. Cir. 2014); *Exergen Corp. v. Thermomedics, Inc.*, 132 F. Supp. 3d 200, 207 (D. Mass. 2015).

[the cell-free DNA]” were all well-understood and conventional—much like the physical steps of PCR/amplification, sequencing, and genotyping here. *See Genetic Techs.*, 818 F.3d at 1377-78; *Ariosa*, 788 F.3d at 1377.

This is why, in *Ariosa*, the court evaluated whether it was “well-understood, routine, and conventional activity” to combine the recited method steps to detect DNA in blood *generally*, not whether it was routine to apply those steps to a particular kind of DNA—*maternal and fetal cfDNA*—which was the natural phenomenon at issue there. *Ariosa*, 788 F.3d at 1377.

The Federal Circuit’s *In re BRCA* opinion is illustrative as well. There, the court concluded that the claims, directed to the abstract idea of comparing various DNA sequences, were not rendered patentable by the recitation of limitations that did “nothing more than spell out what practitioners already knew—how to compare gene sequences using routine, ordinary techniques,” such as “detecting,” “amplification,” and “sequencing.” *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755, 764 (Fed. Cir. 2014). Accordingly, the Federal Circuit found that simply limiting those standard techniques to the field of use of a particular gene was insufficient to confer patentability. *Id.*

Here, likewise, there is no inventive concept sufficient to confer patentability. The only thing the claims add to the standard laboratory techniques they recite is a limitation to a particular natural phenomenon—transplant DNA that



circulates in the blood of a transplant recipient—which as the cases above demonstrate, is insufficient to confer patent eligibility.

**C. The Claims Of The Patents Are Analogous To Diagnostic Claims The Supreme Court And Federal Circuit Have Uniformly Invalidated**

As this Court has recognized, “[t]o determine whether claims are directed to an abstract idea courts generally ‘compare the claims at issue to those claims already found to be directed to an abstract idea in previous cases.’” *In-Depth Test, LLC v. Maxim Integrated, Prods., Inc.*, C.A. No. 14-888-CFC, 2018 WL 6617142, at \*4 (D. Del. Dec. 18, 2018) (quoting *Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327, 1334 (Fed. Cir. 2016)). Here, the analogous cases show that the claims of the Patents are directed to a natural phenomenon just as all other diagnostic claims invalidated by the Supreme Court and Federal Circuit have been. *See Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 952 F.3d 1367, 1371 (Fed. Cir. 2020) (“Under *Mayo*, we have consistently held diagnostic claims unpatentable as directed to ineligible subject matter.”).

In *Mayo*, the Supreme Court invalidated claims setting “forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a [] drug will prove ineffective or cause harm.” 566 U.S. at 77. Here too, the ’652 claims set forth laws of nature—namely relationships between the amounts of donor-specific cfDNA detected in the blood



and the likelihood that a transplanted organ is being rejected or failing.

In *Athena*, the Federal Circuit found methods for detecting auto-antibodies produced in patients to be “directed to” a natural law, instructing that “[c]laiming a natural cause of an ailment and well-known means of observing it is not eligible for a patent because such a claim in effect only encompasses the natural law itself.” 915 F.3d at 752-53. Similarly, here, the Patents claim a natural correlation to an ailment—increased levels of transplant donor-specific cfDNA circulating within a transplant recipient—and only well-known means of observing it.

In *Ariosa Diagnostics*, the Federal Circuit found claims for detecting naturally occurring fetal cfDNA in a pregnant woman’s blood using “method steps [that] were well-understood, conventional and routine” to be directed to a natural phenomenon. 788 F.3d at 1376-77. Here, as well, the claims of the ’497 and ’607 patents recite detecting naturally occurring quantities of donor-specific cfDNA in a transplant recipient’s blood without reciting any improvement over the well-understood, conventional, and routine detection methods recited in the claims.

In *Cleveland Clinic*, the Federal Circuit found that claims for detecting “elevated levels” of a molecule called “MPO,” and the correlation of MPO to the effectiveness of certain drugs, were “directed to” a natural phenomenon. The court found they were not directed to a patentable laboratory method for detecting MPO because “[t]he specifications of the testing patents confirm that known testing

methods could be used to detect [the natural phenomenon], and that there were commercially available testing kits for [the natural phenomenon] detection.” 859 F.3d at 1361. The same is true here, where the Patents’ claims recite detecting elevated levels of donor-derived cfDNA in a transplant recipient’s blood, but again recite no improvements over the known – and commercially available – methods recited in the claims.

And in *Genetic Techs. Ltd. v. Merial L.L.C.*, the Federal Circuit invalidated a claim for detecting compilations of genetic sequences. The Court found that it was “directed to” a natural law because it “does not purport to identify novel detection techniques.” 818 F.3d 1369, 1374-76 (Fed. Cir. 2016). Similarly here, the Patents claim methods for detecting selected compilations, or profiles, of genetic sequences (polymorphisms or SNPs) in cfDNA of a transplant recipient without identifying any new or improved techniques for the detection.

In two recent life sciences cases, the Federal Circuit upheld the patentability of certain claims. *See Rapid Litig. Mgmt. Ltd. v. CellzDirect*, 827 F.3d 1042 (Fed. Cir. 2016); *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 2020 U.S. App. LEXIS 8327 (Fed. Cir. Mar. 17, 2020). But those cases do not apply here for at least three reasons.

First, unlike here, none of the claims at issue in *CellzDirect* or *Illumina* were directed to conventional means for detecting or diagnosing a natural phenomenon.

If they were, the *Illumina* court indicates that they would have been unpatentable. *Illumina*, U.S. App. LEXIS 8327, at \*9 (“Under Mayo, we have consistently held diagnostic claims unpatentable as directed to ineligible subject matter.”).

Second, the result of practicing any of the claims upheld in *CellzDirect* or *Illumina* would be a “preparation” that does not exist in nature – be it a fraction of cfDNA smaller than what is normally found in blood circulation as in *Illumina, id.*, or a select population of liver cells that can survive being frozen and thawed multiple times as in *CellzDirect*, 827 F.3d at 1050-1051. By contrast, the claims of the Patents only detect a natural phenomenon – donor-specific cfDNA – as it exists in nature.

Third, in each of *CellzDirect* and *Illumina*, the Federal Circuit recognized the recitation of new and improved laboratory techniques. *See, e.g., CellzDirect*, 827 F.3d at 1046, 1048 (“Repeating a step that the art taught should be performed only once can hardly be considered routine or conventional”); *Illumina*, U.S. App. LEXIS 8327 at \*11 (finding patents recite “methods for preparing a fraction of cell-free DNA by the physical process of size discriminating and selectively removing DNA fragments longer than a specified threshold” not previously used).

No such new or improved techniques are presented in the Patents, as discussed above, nor do they purport to recite creation of anything unnatural. Notably, the Federal Circuit itself in *Athena* and *Cleveland Clinic* has

distinguished *CellzDirect* on grounds that apply equally here. *See Cleveland Clinic*, 859 F.3d at 1361 (distinguishing *CellzDirect*); *Athena*, 915 F.3d at 751-52 (same); section V.A.2 above (demonstrating standard use of Patents' recited laboratory methods).

## VI. CONCLUSION

There is no inventive concept that renders the Patents' claims to detecting and quantifying transplant cfDNA in a recipient's blood patentable. The claims recite only standard DNA detection and quantification techniques, and do not purport to improve upon or make something innovative out of them. Natera requests that the Court dismiss the FAC in its entirety with prejudice.

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April 9, 2020

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## **CERTIFICATE OF COMPLIANCE**

I hereby certify that this brief has been prepared in Times New Roman 14-point typeface using Microsoft Word, and contains 4,700 words as determined by the Word Count feature of Microsoft Word.

April 9, 2020

*/s/ Derek J. Fahnestock*

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Derek J. Fahnestock (#4705)

### **CERTIFICATE OF SERVICE**

I hereby certify that on April 9, 2020, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on April 9, 2020, upon the following in the manner indicated:

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# **Exhibit 9**

**Redacted in Its Entirety**



# **Exhibit 10**

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# **Exhibit 11**

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# **Exhibit 12**

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# **Exhibit 18**

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# **Exhibit 19**

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# **Exhibit 20**

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## **Exhibit 21**



## UNITED STATES PATENT AND TRADEMARK OFFICE

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## NOTICE OF ALLOWANCE AND FEE(S) DUE

110711 7590 01/11/2019  
 Natera, Inc.  
 201 Industrial Road  
 Suite 410  
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EXAMINER	
MUMMERT, STEPHANIE KANE	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 01/11/2019

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/918,544	10/20/2015	Bernhard Zimmermann	N.012.US.05	9913

TITLE OF INVENTION: METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1000	\$0.00	\$1000.00	\$0	04/11/2019

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.**

**THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.**

**HOW TO REPLY TO THIS NOTICE:**

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

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(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/918,544	10/20/2015	Bernhard Zimmermann	N.012.US.05	9913

TITLE OF INVENTION: METHODS FOR SIMULTANEOUS AMPLIFICATION OF TARGET LOCI

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1000	\$0.00	\$1000.00	\$0	04/11/2019

EXAMINER	ART UNIT	CLASS-SUBCLASS
MUMMERT, STEPHANIE KANE	1637	435-006120

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5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

**NOTE:** Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

**NOTE:** If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

**NOTE:** Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

**NOTE:** This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature \_\_\_\_\_

Date \_\_\_\_\_

Typed or printed name \_\_\_\_\_

Registration No. \_\_\_\_\_



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/918,544	10/20/2015	Bernhard Zimmermann	N.012.US.05	9913
110711	7590	01/11/2019	EXAMINER	
Natera, Inc. 201 Industrial Road Suite 410 San Carlos, CA 94070			MUMMERT, STEPHANIE KANE	
			ART UNIT	PAPER NUMBER
			1637	
DATE MAILED: 01/11/2019				

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**  
 (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

## OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

### Privacy Act Statement

**The Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.



<b>Notice of Allowability</b>	<b>Application No.</b> 14/918,544		<b>Applicant(s)</b> Babiarz et al.	
	<b>Examiner</b> STEPHANIE K MUMMERT		<b>Art Unit</b> 1637	<b>AIA Status</b> Yes

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--**

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 11/15/18.  
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on \_\_\_\_.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on \_\_\_\_; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are 1 and 3-20. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see [http://www.uspto.gov/patents/init\\_events/pph/index.jsp](http://www.uspto.gov/patents/init_events/pph/index.jsp) or send an inquiry to [PPHfeedback@uspto.gov](mailto:PPHfeedback@uspto.gov).

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a) ☐ All      b) ☐ Some      \*c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.

3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\* Certified copies not received: \_\_\_\_.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.  
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.  
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date \_\_\_\_.

**Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. <input type="checkbox"/> Notice of References Cited (PTO-892) 2. <input checked="" type="checkbox"/> Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date <u>11/15/18; 11/16/18</u> . 3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit of Biological Material _____. 4. <input checked="" type="checkbox"/> Interview Summary (PTO-413), Paper No./Mail Date. <u>20181224</u> .	5. <input type="checkbox"/> Examiner's Amendment/Comment 6. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance 7. <input type="checkbox"/> Other _____.
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/STEPHANIE K MUMMERT/  
Primary Examiner, Art Unit 1637

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***Notice of Pre-AIA or AIA Status***

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114.

Applicant's submission filed on November 15, 2018 has been entered.

Applicant's response filed November 15, 2018 is acknowledged. Claims 1 and 3-20 will be examined.

***Inventorship – Correction of Inventorship***

In view of the request to correct inventorship under 37 CFR 1.48 and the accompanying papers, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been previously corrected in compliance with 37 CFR 1.48 (c). The inventorship of this application has been changed by adding inventors, correcting the names of the inventors or the address information.

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However, it has been noted that there are two inventors that were included in the Application Data Sheet filed October 20, 2015 that were not included in the ADS filed on January 4, 2016 and December 15, 2016. These inventors are Phillippe Lacroute and Michael Dodd. Applicant must file a corrected Application Data Sheet together with the required fees to include these inventors.

Following Applicant's response, the application will be forwarded to the Office of Patent Application Processing (OPAP) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

#### ***Information Disclosure Statement***

The information disclosure statement (IDS) submitted on November 15 and 16, 2018 were filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

#### ***Allowable Subject Matter***

Claims 1 and 3-20 allowed.

#### ***Reasons for Allowance***

The following is an examiner's statement of reasons for allowance:

First, it is noted that the rejections over obviousness-type double patenting have been overcome in view of Applicant's amendments to the claims to incorporate the limitations of original claim 2 into independent claim 1.

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Further, it is noted that the instant method step 1 include features of primer concentration, melting temperature of the primers included in the pool of more than 1000 non-identical primers and the length of the starting template nucleic acids at step 1 are key features in achieving the high level of multiplex achieved with the multiplexed primer set. It is also important to note that the amplification products achieved in step 2 are produced in view of a combination of specific features, including the use of a long annealing step greater than 10 minutes, selection of primers which achieve short amplicon sizes as claimed at less than 100 bp in length, and which achieve specific amplification for target loci in at least 50% of the 1000 different loci. These features, at both step 1 regarding the initial target sample and primer composition and step 2 which encompasses the selection of primers and the production of amplicons, are key to the success of the method as claimed.

Finally, it is noted again that while there are references that teach high level multiplex amplification as claimed, none of the prior art teaches the level of multiplex or the specific features as noted above with a priority date that is earlier than the date claimed in the instant claims. The prior art does not teach a high level multiplex of amplification of more than 1000 targets simultaneously prior to 2011. Therefore the claims are free of the prior art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

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***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE KANE MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F 9:00-5:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

**/STEPHANIE K MUMMERT/  
Primary Examiner, Art Unit 1637**

SKM

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